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A.M.A. Journal OF
DISEASES of CHILDREN

Viral Infections in the Embryo

J. M. ADAMS, M.D.
H. D. HEATH, Ph.D.
D. T. IMAGAWA, Ph.D.
M. H. JONES, M.D.
and
H. H. SHEAR, Ph.D., Los Angeles

The concept that viral infections of the mother during gestation may adversely affect the developing young had been accepted with considerable reluctance until the papers by Gregg [1] and Swan * appeared. Since Gregg's report in 1942 on the frequency of abnormalities in children born of women who had contracted rubella during early pregnancy, there have been many confirming reports. Surprisingly little evidence has turned up in the past 10 years, however, to incriminate other diseases as causing abnormalities when they infect the mother early in pregnancy. There are several possible explanations for this fact. First, most of the easily diagnosed virus diseases, such as rubeola, mumps, and chicken pox, occur as a rule in childhood before the normal child-bearing period. Most of these diseases confer immunity, and consequently the incidence of their occurrence in young adults is rather rare. Rubella, on the other hand, does not appear to confer solid immunity and is one of the virus diseases which may recur and can be readily diagnosed in young adults. Because of the rather characteristic rash it is probably quite natural that it should have been the first to have been discovered as a possible cause of congenital abnormalities. However, there are many virus diseases other than rubella which might occur in young pregnant women for which we have no easy clinical means of diagnosis. We refer to the early and mild forms of poliomyelitis with or without paralysis, influenza A, B, and C, and common respiratory viruses, particularly the RI (respiratory infection) group of Hilleman [4] and the new APC (adenoidal-pharyngeal-conjunctival) agents isolated by Rowe and co-workers,[5] Berge,[6] Jawetz,[7] and others. Many of these agents are known to infect young adults, and we recognize a clinical spectrum of infections which accounts for a very mild illness in some patients, whereas other patients may suffer severe infection associated with atypical or viral penumonia. It is the mild or inapparent illnesses which we believe may be responsible for damage

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Read at the Ninth Annual Session of the American Academy for Cerebral Palsy, Oct. 10, 11, and 12, 1955, Memphis, Tenn.

Aided in part by research grants from United Cerebral Palsy Association (PL 33 C1), and the National Institutes of Health, Public Health Service (B-547).

From the Departments of Pediatrics, Infectious Diseases, and Anatomy, School of Medicine, University of California, Los Angeles, and the Veterans Administration Hospital, Long Beach, Calif.

Professor and Chairman of Pediatrics (Dr. Adams); Assistant Research Embryologist, Departments of Pediatrics and Anatomy (Dr. Heath); Assistant Professor of Pediatrics and Infectious Diseases (Dr. Imagawa); Associate Professor of Pediatrics (Dr. Jones), and Assistant Research Virologist, Departments of Pediatrics and Infectious Diseases (Dr. Shear), University of California Medical School at Los Angeles.

* References 2 and 3.

to the fetus when the mother has these infections early in the course of her pregnancy. Although the infection may be extremely mild for the mother, it may not be so mild for the fetus which is in the early stages of morphogenesis with growth taking place at an extremely rapid rate. It has been recognized for some time that embryonic and rapidly growing tissues are highly susceptible to infection and damage by toxic agents. Krugman and Ward [8] showed that rubella may occur without a rash and be very mild indeed. This is an important contribution to our understanding of this particular syndrome. There are reported incidents of mothers who were not known to be ill but who were in the early stages of pregnancy when their older children had rubella, and the baby has shown the characteristic anomalies following birth.

It is known and recognized from clinical as well as experimental studies that many infections, particularly those occurring early in pregnancy may cause a high rate of abortion. This has been successfully demonstrated in human beings at times of influenza and poliomyelitis epidemics. Bland [9] reported that interruption of pregnancy occurred in 58% of his patients whom he studied in 1919 following the pandemic of influenza. A subsequent report by Harris [10] showed a greatly increased rate also with interruption of pregnancy occurring in 39% of his reported cases. Baker and Baker [11] reported that 30% of patients with poliomyelitis aborted at periods varying from six weeks to six months of pregnancy. Aycock and Ingalls [12] reported a ninefold increase in congenital abnormalities when poliomyelitis occurred in the first four months of pregnancy. In the experimental literature Knox [13] reported on murine strains of poliomyelitis causing abortion rates in mice when infected on the first day of gestation as varying from 72% to 88%. After midterm, the abortion rate was rare. Byrd [14] likewise showed with Lansing murine strains that virus was found in the fetuses, suggesting that it crossed the placenta in the mouse, and he also reported a high abortion rate in the animals. Howell, Winters, and Young [15] have likewise demonstrated an increased abortion rate in mice infected with swine influenza virus during gestation, particularly when inoculated five days following breeding. They showed that the rate was much higher in the animals inoculated early as opposed to those inoculated in the middle or in the latter half of pregnancy. There is support then for the concept that moderate to severe infections early in pregnancy will cause abortion. However, if the infection is mild enough and abortion does not result, there are several possible courses which may follow: (*a*) the offspring may develop normally and be born at term with no detectable evidence of abnormalities, (*b*) it is conceivable that there may be mild changes which would manifest themselves later in infancy or childhood, or (*c*) the baby may be born with congenital abnormalities of varying degree.

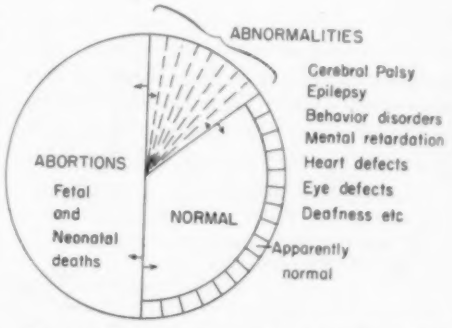

Fig. 1.—Diagram representing a concept of the spectrum of fetal involvement subsequent to maternal infection.

Figure 1 illustrates in graphic form the concept which we have attempted to present. The arrows are included in the figure to point out the extreme variability which may occur in each of the categories according to the type of agent with which we may be dealing. We know, however, in the case of rubella that the area indicated for abnormalities would be large. For other virus infections it might be quite small indeed, or

even absent, but we have very little accurate information concerning this point.

In this paper we are reporting the results of animal experiments in which mice were inoculated with a human strain of influenza just after mating. Not only was the pregnancy rate reduced but evidence of abnormalities in the fetuses was increased. Likewise we shall refer to recent studies in chick embryos in which abnormalities induced by influenza viruses were successfully neutralized by specific antiserum, and death of the embryo was prevented.

Swiss albino mice were bred immediately after intranasal inoculation with a sublethal dose of influenza virus. When the animals were killed at approximately 18 days of gestation, 168 live embryos were present in 20 mice of the virus infected group, as opposed to 190 live embryos in 20 control animals. In the virus infected group, there were 10 dead embryos and in the controls there were 5 deaths. Among the 10 deaths of the virus group, 2 animals were smaller than normal, 1 was curled and shorter than normal, 2 showed abnormalities in the cephalic area, and there were 5 resorbed embryos. Among the five dead controls, one was small, one was normal, and three were resorbed. No true anomalies or abnormalities were observed in the control group. In a similar experiment in which mice were inoculated after being mated for four days, there were 30 abnormal fetuses or implantation sites and 114 normal embryos. In contrast, in the control group there were 17 such abnormalities and 130 normal embryos. The above groups were composed of a random sample of 14 pregnant animals in each.

Figure 2 illustrates four abnormal implantation sites and a normal fetus from the same uterus of an experimental animal. No conclusion can be drawn as yet from these preliminary mammalian studies. There remain many technical problems to solve, such as the time to inoculate with respect to the onset of pregnancy, the amount of virus which will not destroy the fetus and which may be teratogenic, and the proper time to kill the animals in order to determine the extent of the damaging effects.

Although developmental defects in chick embryos induced by influenza virus have been previously reported,[16] the neutralization of teratogenic and lethal effects was accomplished in our laboratories by specific antiserum.[17] Embryonated hen's eggs which had been incubated for 48 hours were candled to determine the position of the blastoderm, and the air sac was collapsed by gentle suction. An opening was cut through the shell, and under 12 × magnification the test and control solutions were injected through the vitelline membrane immediately covering the embryo. This was accomplished by means of a 30-gauge needle

Fig. 2.—*a*, Section of uterine wall from a pregnant mouse killed near delivery following intranasal inoculation with lethal dose of influenza-A (PR8) virus, showing four abortive areas of implantation. *b*, Normal fetus from same uterus as *a*.

Fig. 3.—Chick embryos after 3 days of incubation. Control embryo at left (*a*) shows normal axial curvature and brain development. Infected embryo at right (*b*), inoculated one day previously with influenza-A virus, shows characteristic axial flexion, amnion retardation, and beginning brain damage.

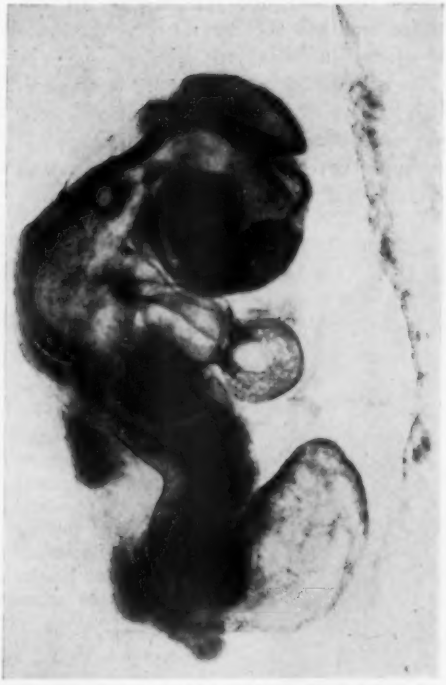

Fig. 4.—Infected chick embryo after four days of incubation, showing micrencephaly, axial flexion, and eye damage occurring during the two days following inoculation with influenza-A virus.

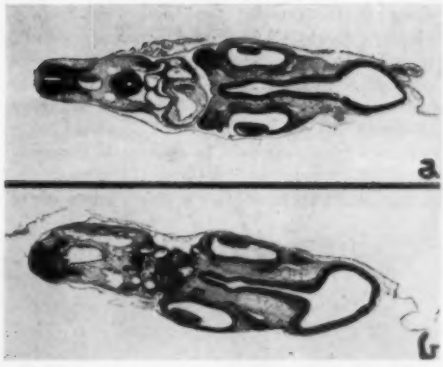

Fig. 5.—Microscopic section of infected embryo is shown in *b* illustrating the diseased spinal cord, general distortion, and flattened amniotic membranes. A normal embryo is illustrated in *a*.

and a 0.25 cc. syringe combined with a specially designed dispensing apparatus which permitted the injection of 0.03 ml., the standard volume used throughout the study. After inoculation, the opening in the shell was sealed with Scotch tape and routine precautions against infection were observed at all times. Daily observations of the embryos were made by temporarily removing the Scotch-tape window. The appearance of the body flexion and

micrencephaly, characteristic of influenza infection 24 hours following inoculation, is shown in Figure 3, *b* in comparison with the normal morphology, Figure 3, *a*, at the same stage of development. After 48 hours, the mesencephalon and telencephalic hemispheres were typically almost completely collapsed. The eyes were frequently flattened and misshapen, and the auditory vesicles sometimes appeared compressed (Fig. 4). Microscopic sections of the infected embryos revealed a distorted and abnormal spinal cord, and the amniotic membranes were thin and flattened. These changes are illustrated in Figure 5.

The results of virus titrations indicate that concentrations of virus as low as 10^{-6} were capable of producing abnormalities and death of the embryo. Embryos which received noninfected allantoic fluid developed normally. In most experiments 10^{-4} concentration of virus was employed as the standard test inoculum because it produced teratogenic and lethal effects uniformly. Virus was recovered from all of the suspensions which were prepared from dead embryos with typical anomalies.

Dilutions of antiserum as high as 1:800 completely protected all embryos against both the teratogenic and lethal effects following injection after mixture with the virus in vitro. This result did not occur when either normal rabbit serum or control medium was substituted for immune serum. When immune serum was diluted to 1:6400 or higher, neutralization failed to occur. In neutralization studies *in ovo*, antiserum, although effective, was not capable of preventing the pathogenic effects of the virus in all cases. The optimum protection was obtained when antiserum was administered before virus inoculation. The protective effect was less marked when immune serum was given one, two, or five hours after virus injection, and it practically disappeared when serum therapy was delayed until eight hours after virus injection. The control group exhibited 100% incidence of anomalies and death.

Summary and Conclusions

A brief review of the literature on viral infections in the embryo, and a concept of a spectrum of involvement of the embryo have been presented. The concept suggests that severe infections in the embryo result in death, while mild infections may produce abnormalities or the fetus may be born apparently normal. In mice which were infected with a human strain of influenza virus, a decrease in the pregnancy rate and an increase in fetal abnormalities were produced.

The teratogenic and lethal effects produced by infection of early chick embryos with influenza A virus was prevented by specific immune serum.

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Primary Pulmonary Vascular Disease with Cor Pulmonale

Report of Three Cases in Children, One with Congenital Hypertension and Two Siblings with Allergic Vasculitis and Disorders of Skeletal Epiphyses

P. J. BARNARD, M.D.
and
J. G. A. DAVEL, M.A., M.Sc., M.R.C.P., F.R.C.S.(Ed.), Pretoria, Union of South Africa

In the first case here described there was holdover of fetal pulmonary arterial structure with hypertension and cor pulmonale. There were also distinctive segmental arterial lesions and foci of interstitial pneumonia. Arterial lesions outside the lungs were not found. The other two cases were brothers who died of cor pulmonale due to allergic vasculitis confined to the lungs. In addition, one had Perthes' disease and the other dysplasia epiphysalis multiplex.

The first case is presented because cor pulmonale was primarily due to congenital hypertension and because there were distinctive lesions of intrapulmonary arteries. In such lesions capillaries had developed segmentally in arterial walls without apparent other damage, since smooth muscle of the media between capillaries was largely intact. Additional features of this first case were livedo reticularis, syndactyly, fibrosis around hair follicles, and congenital deformity of intramyocardial arteries. The other two cases are recorded because allergic vasculitis limited to pulmonary vessels in siblings in association with epiphyseal disturbances has not, to our knowledge, been previously described and because there were also segmental arterial lesions with development of capillary networks. Such segmental lesions were, however, accompanied by inflammatory destruction of the media, whereas in the first case this coat had been largely preserved. In these other two cases capillaritis of alveolar walls closely resembling the glomerular capillaritis of acute diffuse Bright's disease was also found.

Submitted for publication May 1, 1956.

From the Departments of Pathology and Paediatrics, University of Pretoria.

Report of Cases

CASE 1.—*History.*—A European girl aged 7½ years came to hospital with the story that her skin had been disfigured from birth by a network of blue vessels, that she had been short of breath after feedings and that she had been subject to attacks of syncope. These attacks began at the age of 9 months and gradually declined from a frequency of two or three a week to disappear at the age of 5 years. Attacks were preceded by headache, dizziness, and rapid heart beat according to the mother but without tremors or fits while unconscious, a state that lasted from a few minutes up to half an hour. Seven months prior to admission her eyes, limbs, and abdomen became swollen, signs that had fluctuated in severity since then. At this time she had also had attacks of precordial pain severe enough to make her cry. Pain came on especially at night, left her exhausted, and was not specifically related to exercise. Four months before admission she contracted whooping cough, measles, and chicken pox in swift succession, and she began to go bald. An unproductive cough had persisted from this time on until her death about six weeks after admission to hospital. Shortly after recovery from the infectious illnesses mentioned, worm-like movements of the left arm and paralysis of the left leg arose. This gradually improved until she had regained partial use of these limbs.

Physical Examination.—There was dyspnea, swelling of the eyelids, and livedo reticularis of her whole body (Fig. 1). The scalp was swollen and bore only fine, sparse hair. Hemorrhage had occurred from some of the dilated veins. The

Fig. 1. (Case 1).—Generalized livedo reticularis.

fontanelles were closed, and though the neck seemed short it had normal mobility. Her height, weight, and head circumference were all moderately below normal averages. The pulse was 140 per minute, of small volume and regular rhythm. The heart was thought to have enlarged to the right. A Grade 2 systolic murmur was heard over the precordium and the second pulmonic sound was accentuated. Blood pressure was 115/70. Signs of consolidation were present over the right, upper, and middle lung lobes, and crepitations were heard over both lung bases posteriorly. The liver had enlarged 4 fingerbreadths below the costal margin but without signs of ascites or palpable splenic enlargement. There was slight edema of the ankles and presacral region. The left leg was paretic, and the left arm adducted with tendency to athetosis. Voluntary movements were performed with difficulty.

Special Investigations.—Blood protein values were as follows: total 5.9 gm/100 cc., albumin 3.1, and globulin 3.4. Chest roentgenograms showed great cardiac enlargement and consolidation of the right upper lobe. The electrocardiogram demonstrated right ventricular hypertrophy and peaked P waves in standard lead II. Cardiac catheterization (Dr. A. Brink) gave the following pressures in millimeters of Hg: S.V.C. 26/19, R.A. 27/17, R.V. 110/21, pulmonary artery 141/29, and right pulmonary artery 143/73. Femoral arterial blood had an oxygen saturation of 69%.

Postmortem Examination.—Apart from small amounts of transudate in the main serous cavities and passive venous congestion of the abdominal viscera, abnormalities of the internal organs were confined to heart, lungs, and brain. The heart showed isolated right ventricular hypertrophy and dilatation. Right ventricle weighed 87 gm., left ventricle 40 gm., and mean thicknesses of these chambers were, respectively, 7 and 10 mm. Antemortem clot filled the left atrial appendix. The ductus arteriosus had closed, but the foramen ovale was open and 3 mm. in diameter. Adhesions united upper and middle lobes of the right lung with the chest wall. These lobes were firmly consolidated. The lower lobe was not consolidated, but its cut surface showed a network of thickened interlobular septa. Upper lobe of the left lung was unevenly consolidated; the lower, evenly consolidated. The intrapulmonary arteries of both lungs were diffusely thickened, more so in consolidated regions. An old wedge-shaped infarct 1.0×1.0×0.5 cm. in cross-section occupied the right internal capsule of the brain.

Microscopically, endocardium of the left atrium was thickened by fibroelastosis. Both segments of the mitral valve showed capillarized scars. One myocardial scar was encountered in the left ventricle and in a few scattered places collections of lymphocytes were present interstitially. Fibrinoid

Fig. 2 (Case 1).—Coronary artery of the interventricular septum. Its thick muscular wall consists of a thin inner circular layer and a thick outer longitudinal layer. Weigert-van Gieson stain, × 275.

Fig. 3 (Case 1).—Coronary artery of left ventricle with inner longitudinal and outer circular layers. At 12 o'clock the space between internal elastic lamina and the medial coat is occupied by smooth muscle and fibrous tissue in disorderly arrangement. Weigert-van Gieson, ×144.

change and Aschoff follicles were not found. Some small coronary arteries had thick muscular coats composed of circular and longitudinal layers, the circular layer sometimes situated inside the longitudinal layer, sometimes outside it (Figs. 2 and 3). This deformity was thought to be congenital, since we have encountered it at youthful ages in otherwise normal human and animal hearts.

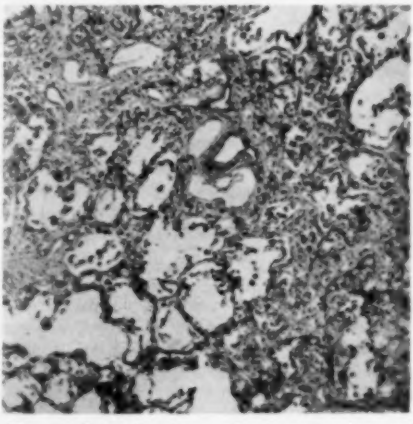

Fig. 4 (Case 1).—Lung showing alveolar walls thickened by connective tissue and infiltrated by chronic inflammatory cells. Hematoxylin and eosin, × 67.

In consolidated lung (Fig. 4) alveolar walls were broadened by reticulin fibers, fragments of collagen, distorted and often thickened elastic fibers, as well as infiltrations of lymphocytes, fibroblasts, and plasma cells in small numbers. Eosinophiles were not encountered. Dilated blood capillaries were numerous. Reticulin and collagen but no organizing fibrin were found in some of the alveolar spaces. These spaces also contained macrophages, and their walls sometimes exhibited cuboidal metaplasia. Emphysema was found only in consolidated lung. Away from regions of consolidation, alveolar walls were normal. Fibrosis had also involved interlobular septa to cause the net-like pattern seen with the naked eye. Mild exfoliation of epithelium, chronic inflammatory cell infiltration without eosinophiles, and capillary congestion were changes found in the bronchi. Fibrinoid necrosis and Aschoff follicles were not encountered in the lungs.

Though arterial lesions were more advanced in consolidated lung, they were of the same types as those occurring elsewhere. Elastic arteries (those of external diameter greater than 1.0 mm.) were sparsely involved by intimal thickenings composed of swollen endothelial cells in an edematous matrix that was either slightly or not at all positive to periodic acid-Schiff (PAS) staining. Most lesions were found in muscular arteries (those of external diameter less than 1.0 mm.) A differential count of the types of lesion present in two sections from each of the lung lobes showed medial hypertrophy and endarteritis fibrosa to be most frequent. Medial hypertrophy was most apparent in small muscular arteries (Fig. 5). There was also widespread pro-

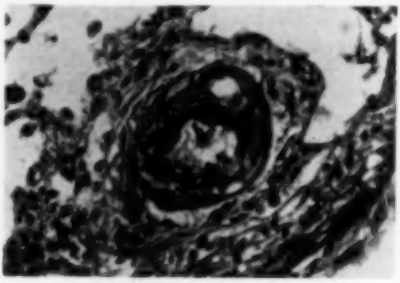

Fig. 5 (Case 1).—A small pulmonary artery with a thick medial coat occupied at one o'clock by a capillary. Weigert-van Gieson, × 275.

liferation of endothelial cells, the nuclei of which were orientated either radially or concentrically. The latter arrangement commonly contributed to the appearance of the lesion known as hyperplastic arteriolar sclerosis (Fig. 6). Intimal deposition of collagen varied in amount from a trace to almost complete obliteration of the lumen. This was usually accompanied by deposition of elastin as

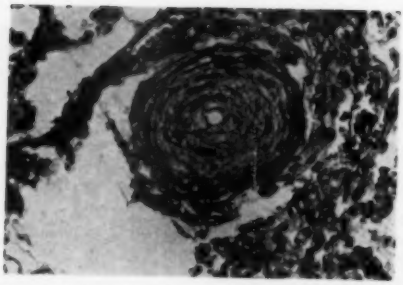

Fig. 6 (Case 1).—Small pulmonary artery with concentrically proliferated endothelium producing a lesion like the hyperplastic arteriolar sclerosis of systemic hypertension. Weigert-van Gieson, × 220.

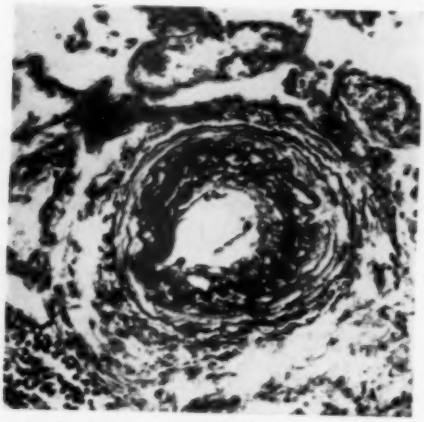

Fig. 7 (Case 1).—Fibroelastosis of a small pulmonary artery. Weigert-van Gieson, × 220.

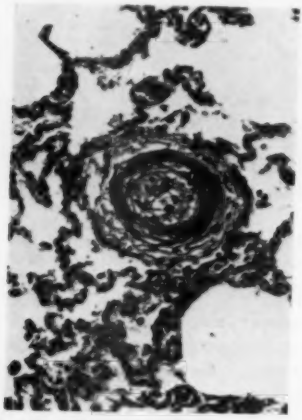

Fig. 8 (Case 1).—Hyaline arteriolar sclerosis and intimal proliferation. Hematoxylin and eosin, × 144.

well, either eccentrically or circumferentially, to produce the lesion known as elastosis (Fig. 7). Other sparsely distributed lesions were those of hyaline arteriolar sclerosis (Fig. 8.) Hyperplastic arteriolar sclerosis, elastosis, and hyaline arteriolar sclerosis are all lessions associated with severe hypertension, whether of the pulmonary or of the systemic circulation. Another common arterial lesion in this case was segmental capillarization (Figs. 9 and 10). It was studied in serial sections

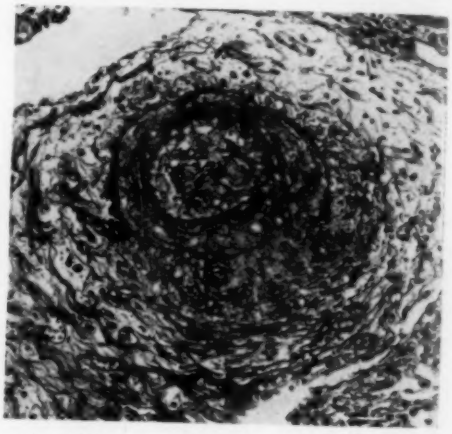

Fig. 9 (Case 1).—Segmental capillarization showing medial coat to be otherwise intact. Weigert-van Gieson, × 144.

cut at 4 microns and stained Weigert-van Gieson. Capillarization was seen only in muscular arteries and was present in both consolidated and nonconsolidated lung. Affected segments were occupied by capillaries, the endothelial cells of which were swollen and often several layers thick. Smooth muscle of the medial coat between capillaries was intact. Though capillarization was sometimes confined to media, it commonly involved adventitia as well. Capillaries also rarely communicated by minute openings in the internal elastic lamina with the lumen or with recanalized endothelium of fibrosed intima. Adventitial capillarized tissue was followed in one series of sections for a distance of 400 microns, after which it ended without anastomosing with other vessels of the lung. Elastic arteries were commonly surrounded by broad zones of fibrosis containing dilated capillaries.

The pleura was occupied by an extensive system of large and small intercommunicating blood spaces extending along thickened interlobular septa into the lung (Fig. 11). This system consisted of dilated capillaries and veins some of which had ruptured into one another. It was supplied by small sclerosed arteries and it drained into veins with fibrosed intimal coats. Whether

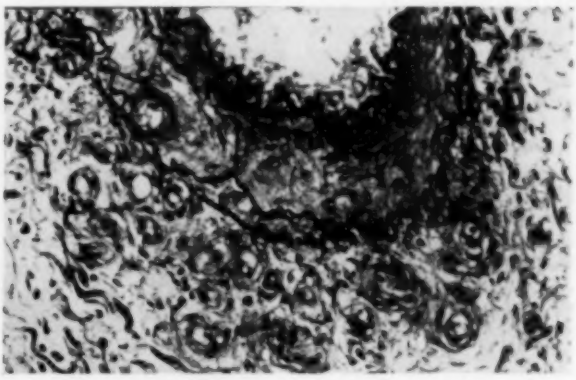

Fig. 10 (Case 1).—Replacement of arterial medial and adventitial coats by capillaries composed of swollen endothelial cells. Weigert-van Gieson, × 220.

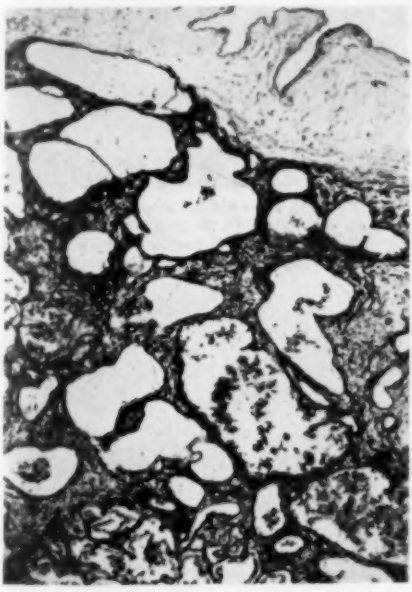

Fig. 11 (Case 1).—A system of dilated subpleural capillaries and veins extending into the lung substance. Incomplete septa in some of these dilated blood spaces suggest that vessels had ruptured into one another. Overlying pleura is edematous. Weigert-van Gieson, × 53.

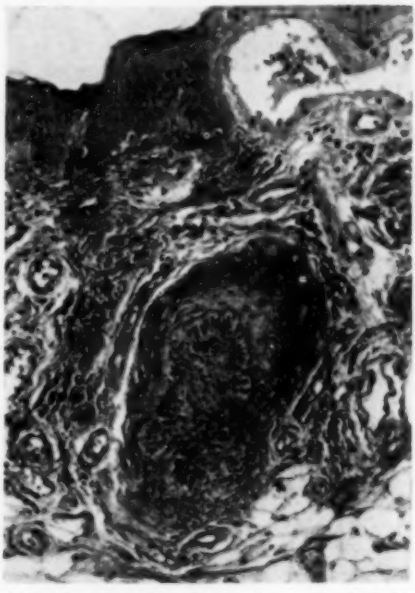

Fig. 12 (Case 1).—Scalp showing endothelial-lined space with thinning of overlying epidermis and fibrous encapsulation of a hair follicle. Weigert-van Gieson, × 144.

this vascular system was due to venous obstruction by interlobular fibrosis or whether it was a pulmonary form of livedo reticularis could not be decided.

Scalp tissue for histological examination was chosen from a region where livedo reticularis had been pronounced (Fig. 12). It was studied in serial sections cut at 10 microns and stained Weigert-van Gieson. The outer third of the corium was occupied by a capillocavernous system of blood-filled spaces that drained by tortuous veins. These spaces contained organizing blood clot in places and appeared to have caused thinning of the overlying epidermis. Deeper in the corium closely packed capillaries with swollen endothelium, unconnected with the capillocavernous network, were also found. There were no arteriovenous anastomoses. Most hair follicles were en-

closed in thick collagen capsules, an abnormality thought to explain the loss of hair noted clinically. Patchy calcification was present deep to the galea aponeurotica.

CASE 2.—*History.*—A European boy aged 6 years 10 months was admitted to hospital with the complaints of dyspnea, weakness, upper abdominal pain, nausea, cough, vomiting, and cyanosis, all more or less of one week's duration. Previous to this he had been in good health except that he tired easily. Former illnesses were measles, mumps, and repeated attacks of tonsillitis. Nine months before this a pediatrician had seen him for his waddling gait and a diagnosis of Morquio's disease was suggested. He found no abnormalities in heart or lungs. An elder brother had died from a condition which the father believed to have been identical with the present case. A postmortem examination had been done and is included in this paper (Case 3).

Physical and Special Examinations.—The child was acutely ill, of small build, and he had pronounced dyspnea with slight cyanosis. He had a fast, regular pulse and was in congestive cardiac failure. Blood examination showed hemoglobin of 15.5 gm/100 cc., a hematocrit of 51%, and a neutrophilic leucocytosis of 13,700/cu. mm. On x-ray examination there was right ventricular enlargement and dilatation of the pulmonary arteries. The only skeletal lesions were healed bilateral Perthes' disease.

Because of the allergic pulmonary vasculitis that had been found postmortem in the elder brother it was surmised that the younger brother had a similar disease. Consequently, he was given cortisone in addition to supportive and symptomatic treatment. He died about six weeks after the advent of cardiac symptoms.

Postmortem Examination.—The main serous cavities contained transudate in moderate amounts. The lungs were pale with normal pleural investments. They had a firm, even consistency and showed some thickening of the intrapulmonary arteries. Right ventricle weighed 35 and left ventricle 19 gm. Right ventricle was 4 mm. thick; left ventricle, 5 mm. Hypertrophy and failure were confined to the right side. The foramen ovale had closed, but the ductus arteriosus admitted a probe 2 mm. thick. Abnormalities in organs other than the heart and lungs were passive venous congestion and tonsillitis.

Microscopically, muscle fibers of the right ventricle were hypertrophied. Elastic arteries of the lungs were sparsely involved by intimal lesions consisting of edematous periodic acid-Schiff-negative ground substance containing scattered fibroblasts. Muscular arteries also exhibited intimal edema, but there was segmental destruction of the medial coat together with fibroblastic activity and formation of capillaries in addition (Fig. 13). Muscular arteries were further involved by a segmental necrotizing arteritis with the stigmata of polyarteritis nodosa (Fig. 14). Lesions taken to represent advanced healing of this necrotising arteritis were segmental capillarized granulomata (Fig. 15). Such capillarized lesions differed, however, from those of the first case in that capillaries were fewer in number and in that the arterial

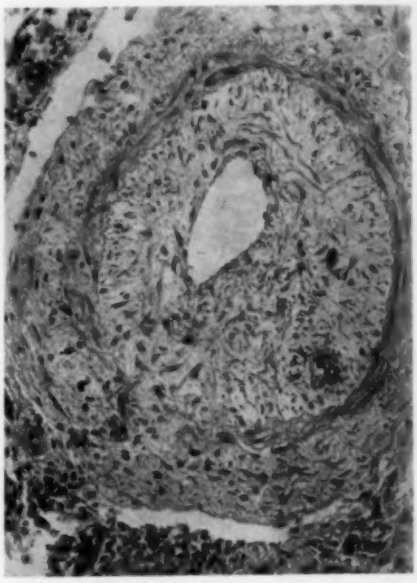

Fig. 13 (Case 2).—Muscular pulmonary artery; edematous intimal and adventitial thickening with segmental destruction of media, early capillarization and fibroblastic activity. Hematoxylin and eosin, ×181.

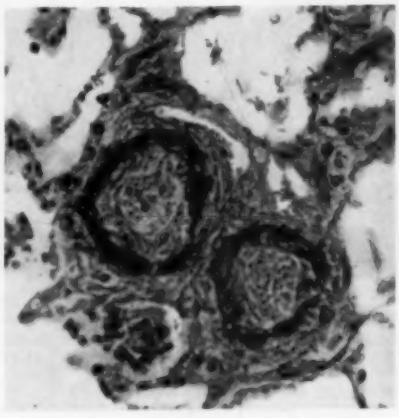

Fig. 14 (Case 2).—Two small pulmonary arteries showing fibrinoid necrosis. Periodic acid-Schiff, × 220.

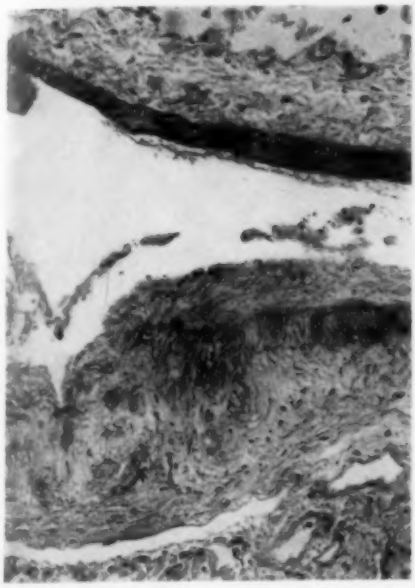

Fig. 15 (Case 2).—Segmental replacement of muscular pulmonary artery by capillarized connective tissue. Hematoxylin and eosin, × 144. (Compare Figs. 9 and 10.)

wall had been destroyed (compare figs. 9 and 10). Arterial media was not hypertrophied and Aschoff follicles were not seen. Precapillary vessels were

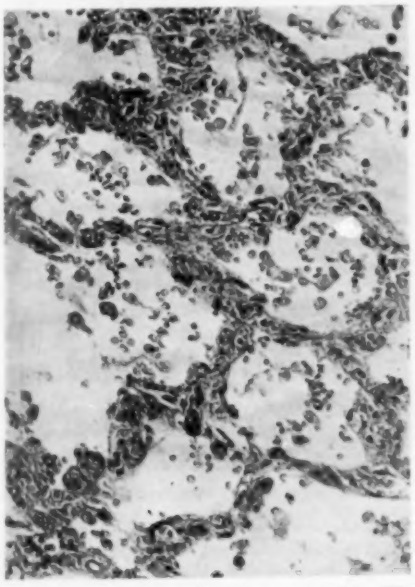

Fig. 16 (Case 2).—Alveolar capillaritis. Weigert-van Gieson, × 220.

diffusely narrowed by endothelial proliferation, a change that must have created a formidable barrier to right ventricular outflow. Alveolar capillaries were similarly involved, but they were infiltrated by neutrophiles and lymphocytes as well (Fig. 16). This capillaritis was similar to that of Case 3, but less pronounced. In regions showing capillaritis, alveolar walls became lined by swollen epithelial-like cells. Alveolar spaces contained macrophages but no fluid exudate or fibrin. The bronchial tree was congested. Organs other than heart and lungs, including skeletal muscle, were normal except for passive venous congestion and chronic tonsillitis. Histologically, a section from the right femoral head was consistent with the diagnosis of Perthes' disease.

Case 3.—This European boy was 10 years of age at the time of death. At age 11 months he was examined by an orthopedic surgeon because he had reverted to crawling after having commenced to walk, but no diagnosis was reached. At three years of age he was once again examined by two orthopedic consultants who both suspected abortive poliomyelitis. Radiographs of the skeleton at this time revealed no abnormalities. The tonsils were removed without any improvement occurring. Late in his ninth year of age he was examined once more and the diagnosis of dysplasia epiphysialis multiplex made. His locomotor disability manifested itself as generalized weakness and deformity of one hip, the leg being swung and dragged along. This ungainliness was ascribed to femoral head and acetabulum not fitting properly. Shortly after this he was admitted to hospital for cardiac failure. Examination by a pediatrician six months before had shown no heart disease though the parents thought his exercise tolerance diminished as compared with children of his own age.

His last illness began three weeks prior to admission, with excessive fatigue and abdominal pain after a bicycle ride. Two weeks later vomiting began which persisted off and on for about seven days. During this time he developed dyspnea and swelling of the face and feet. This swelling subsided during the next few days, but the cyanosis intensified.

As a young child he had mumps, whooping cough, rubella, measles, and bronchitis. He was the first-born of three brothers and weighed 2700 gm. (6 lb.) at birth. Both pregnancy and delivery had progressed normally. He was breast-fed for three months and reached the milestones of infancy in the expected time.

Family History.—After his birth, the mother had separation of the pelvic bones which caused some difficulty in walking. She had had rheumatic fever at the age of 17 years. The father is alive and well. The third brother subsequently developed a similar illness and is here included as Case

2. The second brother has also died and there is the likelihood of consanguinity between the parents but they cannot be traced for further information.

Physical and Special Examinations.—On examination a week prior to death, there was pronounced cyanosis of the lips and extremities. The fingers seemed to be clubbed. Apex beat was displaced beyond the nipple line in the fifth intercostal space, and there was diffuse pulsation over the left precordium. There also was tachycardia, a loud second sound over the base and a suspected diastolic murmur at the same area. Jugular venous pressure was raised and systemic blood pressure was normal. The liver was enlarged. The electrocardiogram showed pronounced right axis deviation, right ventricular hypertrophy, right bundle-branch block, and a large right atrium. Owing to the patient's grave condition, no detailed examination of the joints could be made. During the week following admission to hospital, progressive deterioration with rapid pulse, triple heart sounds, and a systolic apical murmur accompanying the first heart sound set in. Terminally a loud systolic murmur was audible over the entire precordium. It was maximal over the apex but also very loud over the left parasternal area. Death occurred in congestive heart failure, there having been no response whatever to treatment.

Postmortem Examination.—This revealed some wasting and mild generalized cyanosis. There was no dependent edema but the large serous cavities contained transudate in small amounts. The lungs were pale, their consistency evenly firm, and their small arteries thickened. The right ventricle weighed 39 gm. and left ventricle 28 gm. The right ventricle was 6 mm. thick, the left 7 mm.

Histologically, muscle fibers of the right ventricle were hypertrophied. Endocardium and valves were normal. A few small coronary arteries showed anomalous arrangement of smooth muscle like that described for Case 1. Pulmonary arteries of elastic type showed adventitial fibrosis like those of Case 2. Muscular arteries were mostly normal, but, where involved, the lesion was either endarteritis fibrosa or granulomatous destruction without fibrinoid necrosis (Fig. 17). What was taken to be a more advanced stage of this lesion were capillarized granulomata like those illustrated for Case 2 in Figure 15. Aschoff bodies were not encountered. Precapillaries were severely narrowed, as were alveolar capillaries, by endothelial proliferation, a process that obliterated them and thickened alveolar walls (Fig. 18). Occasional capillaries were occluded by hyaline thrombi thought to have been of platelet origin. Neutrophiles and nuclear debris, together with lymphocytes, were scattered among proliferated endothelial cells. This capillaritis imitated closely the glomerular lesion of acute diffuse Bright's disease. Capillary sclerosis and interstitial fibrosis were not observed. The alveolar spaces were free from fluid exudate and fibrin. They were sometimes lined by swollen epithelial-like cells and

Fig. 17 (Case 3).—Segmental granulomatous destruction of a muscular pulmonary artery. Weigert-van Gieson, × 144.

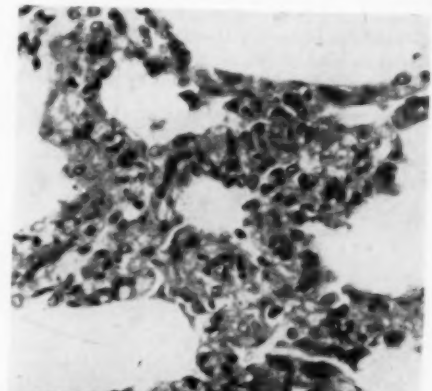

Fig. 18 (Case 3).—Alveolar capillaritis. Hematoxylin and eosin, × 330.

often contained macrophages laden with sudanophilic droplets. The bronchi and the abdominal viscera were passively congested. Skeletal muscle was normal. Epiphyses were not available for histological examination.

Comment

In the first case here described, the course of events has been interpreted as follows. Pulmonary hypertension was congenital because pulmonary arteries had failed to involute after birth as normally happens.[1] Why involution failed to occur is not apparent. The various other arterial lesions, except only segmental capillarization, then arose secondarily as the result of hypertension. Hyperplastic arteriolar sclerosis, elastosis, and hyaline arteriolar sclerosis are expressions of severe hypertension in pulmonary arteries just as they are in systemic arteries.[2] The segmental arterial capillarization was distinctive because smooth muscle of the medial coat was intact, whereas it had been destroyed in the acquired capillarized lesions of the two cases with vasculitis. (Compare Figs. 9 and 10 with Fig. 15.) This particular variety of segmental capillarization might, therefore, have been congenital. If so, it was an anomaly not due to arrest of normal development, since we found nothing similar in the lungs of 12 fetuses aged 4 weeks to 6 months. Neither could it be decided if arterial capillarization was a pulmonary expression of livedo reticularis. It was not encountered in arteries of either scalp or skin, but these structures had been sampled less extensively than the lungs. It is also not known whether the capillocavernous formations within fibrosed interlobular septa had resulted from venous obstruction or whether they represented livedo reticularis of the lungs. The respiratory difficulty that had been present from birth was probably due to congenital hypertension, but not long before death pneumonia of progressive type arose. What caused this pneumonia was not discovered, but possibilities are the Hamman-Rich syndrome, primary atypical pneumonia, and pneumonia due to viruses, rickettsiae, and allergy,* all of which may cause progressive interstitial pulmonary inflammation. In the Hamman-Rich syndrome, apart from interstitial fibrosis, any of the following changes alone or in combination have been described; fibrinous exudation, cuboidal alveolar metaplasia, alveolar hyaline membranes, endothelial hyperplasia, eosinophilic infiltration, alveolar and bronchiolar necrosis, squamous bronchiolar metaplasia, endarteritis fibrosa, and cor pulmonale.† This syndrome can, therefore, be taken to embrace all cases of progressive interstitial pneumonia without a known cause. The pneumonia of this first case fits well into such an accommodating syndrome. Even though fibrinoid change and Aschoff follicles were lacking, rheumatic pneumonia cannot be excluded, since there was thickening of the left atrial endocardium, myocardial scarring with lymphocytic infiltration, and capillarized fibrosis of the mitral valve leaflets. Periodic acid-Schiff and Gram stains of lung sections showed no parasites, fungi, bacteria, or cellular inclusion bodies.

The other two cases died of rapidly advancing cor pulmonale due to arteritis, obliteration of precapillaries, and alveolar capillaritis. In both, vascular disease was confined to the lungs. Our reasons for ascribing the vasculitis to allergy are as follows. Allergic arterial lesions are typically segmental and may be granulomatous in their chronic stages.‡ Endothelial proliferation, not only in arteries but of capillaries, is a common manifestation of vascular hypersensitivity.§ Necrotising arteritis may be caused in animals by sensitising them to foreign protein, and it has been recorded in man as an allergic response to serum and drugs.‖ The pulmonary arteries are involved in about one-third of polyarteritis nodosa cases and more rarely les-

* References 3-6.
† References 7-14.
‡ References 15 and 16.
§ References 17 and 18.
‖ References 19-22.

ions like those of this disease are confined to the lungs, as here described and previously recorded.[23] No specific evidence of rheumatic fever was found. Though it can duplicate the histological picture of these two cases in all particulars, rheumatic fever is itself nowadays regarded as an allergic response of connective tissue. Special stains showed no bacteria, fungi, parasites, or inclusion bodies.

Why vasculitis was confined to pulmonary vessels in these two cases is not known. Of preexistent hypertension, such as holdover of fetal arterial structure, which might have determined such selective localization, there are no evidence. Why vasculitis of a similar type should have affected siblings is no less obscure than why it had been limited to the lungs. These two children had no other form of allergic disease, they had not received serum and there was no history of drug idiosyncracy.

The alveolar capillaritis also found was strikingly similar to the glomerular capillaritis of acute diffuse glomerular nephritis, in that endothelial proliferation, infiltration by inflammatory cells, hyaline thrombosis, and hyperplasia of adjacent epithelium are characteristic of both. In glomerular capillaritis there is hypertension confined to the systemic circulation, and in alveolar capillaritis, as in these two cases, hypertension was confined to the pulmonary circulation. This suggests that in pulmonary ischemia as in renal ischemia a vasopressor substance is liberated that has specific action on the circulation in which it arises.

Summary

Three cases of primary pulmonary vascular disease with segmental development of capillaries in arterial walls and death from cor pulmonale are described. In the first case, a girl aged 7½ years, cor pulmonale was primarily due to holdover of fetal arterial structure with subsequent development of hypertensive arteriosclerosis. Arterial walls had also been replaced segmentally by capillary networks with preservation of smooth muscle between the capillaries. This is thought to be a congenital vascular anomaly not hitherto described. The interstitial pneumonia also found was acquired, but histological examination failed to reveal the cause. Other features of this first case were livedo reticularis, syndactyly, fibrosis around hair follicles, and congenital deformity of intramyocardial arteries.

The other two cases were brothers aged 6 years 10 months and 10 years, respectively, who died of cor pulmonale due to allergic vasculitis confined to the lungs. In addition, the one had Perthes' disease and the other dysplasia epiphysalis multiplex. This association of lesions in siblings is thought to be unique. They also had lesions in which arterial walls had undergone segmental replacement by capillary networks, but these lesions differed from those of the first case in that smooth muscle had been destroyed. In these two cases capillaritis of alveolar walls closely resembling the glomerular capillaritis of acute diffuse Bright's disease was also found.

Dr. A. Brink performed the cardiac catheterization on Case 1, Dr. Ben Epstein provided the clinical details of Case 3, and Mrs. P. J. Barnard provided the histological preparations and photographs. The South African Council for Scientific Research defrayed the costs of this work, and the University of Pretoria provided a publication grant.

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Effect of Supplementing Soybean Proteins with Lysine and Other Amino Acids

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Ever since the recognition of Osborne and Mendel,[1] in the early years of the present century, of the dietary indispensability of certain amino acids, physicians, nutritionists, and others have looked forward to the practical possibility of improving the protein value of certain foods by direct supplementation with specific amino acids. This hope can now be partly satisfied because of the availability of L-lysine, DL-methionine and L-cystine in commercial quantities at a reasonable price. There is no doubt that the addition of lysine to wheat products results in a significant improvement in the nutritive value of the proteins.[2] Likewise, small additions of cystine or methionine improve the protein value of milk, meat, soy, and other leguminous vegetables.[2] However, care must be taken not to allow initial enthusiasm to exceed proved scientific evidence.

The formation of tissue proteins is an "all or none" proposition in the sense that the supply of amino acids for synthetic purposes is utilized only to the extent permitted by that amino acid available in the least amount with reference to the requirements of the protein pattern being synthesized. This means that the amino acid requirements of the growing animal are determined by the amino acid composition of the tissue proteins formed during growth superimposed upon the amino acid needs for the maintenance of the *status quo*. The goal then is to provide the animal with the pattern of (essential) amino acids which it is using. Protein is wasted when this pattern is distorted by furnishing either too little or too much of one or more (essential) amino acids.[3]

Although the slight deficiency in the sulfur amino acid content of soybean proteins is well known, the recent implication that the nutritive value of these proteins could be improved by the addition of L-lysine[4] prompted us to carry out the experiments described below. The results demonstrate that the nutritive value for young rats of the proteins in a widely used soybean infant food (Mull-Soy) can be, if fed at a low level of protein*, slightly improved by the addition of cystine, methionine, or a mixture of them but that the addition of lysine in small quantities was not beneficial and in larger amounts actually suppressed growth.

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* The fact that soy proteins are a little more deficient in methionine than milk is of no consequence in practical infant feeding, for, as Mendel pointed out many years ago, optimal growth and well being can be achieved by supplying a larger quantity of a nutritionally inferior protein than would be necessary with a protein of higher biological value, providing the inferior protein does not show any marked deficiency of an essential amino acid. In fact, calculation will show that Mull-Soy equivalent to 40 calories will supply more than the 90 mg. of lysine per kilogram per day needed by infants. Normally, 110 calories of Mull-Soy are fed per kilogram of body weight per day.

Experimental

Three experiments were carried out at various periods during the year 1955. Since the laboratory is not air-conditioned, certain variations of the absolute rate of growth of the animals is to be expected. The design of each feeding experiment was as follows:

Mull-Soy (spray dried for convenience in feeding) containing approximately 25% of protein (N×6.25) was mixed with U.S.P. XIV salt mixture (3%), vitamins † and sufficient dextrose so that the final diet contained 10% protein (N ×6.25). This diet was fed ad libitum to groups of six male weanling rats for two weeks. The animals were kept in individual cages on the conventional wire screens. A record was made of the individual food consumption and weight of the animals.

† Vitamin supplement per 100 gm. of diet:

2 Methyl-1,4-naphthoquinone	1.0 mg.
Thiamine HCl	0.8 mg.
Riboflavin	1.6 mg.
Pyridoxine HCl	0.8 mg.
Nicotinic acid	4.0 mg.
d-Calcium pantothenate	4.4 mg.
p-Aminobenzoic acid	4.0 mg.
Choline bitartarate	400.0 mg.
Inositol	21.6 mg.
Vitamin B_{12}	3.3 γ
Folic acid	0.1 mg.
Biotin	30.0 γ

Three drops of an oil containing vitamin A (4000 I.U./ml.), vitamin D (800 I.U./ml.) and vitamin E (4.0 mg/ml.) were fed separately once a week to each rat.

Results

TABLE 1.—*Results of Adding Various Levels of Cystine or Methionine to a Soybean Diet Fed to the Rat* Average Weight Gain and Protein Efficiency in Two Weeks

Supplement	% of Protein	Wt. Gain, Gm.	Protein Efficiency, Gm. Gain/Gm. Protein Eaten
None		19.5	1.97±0.16†
Cystine	0.24	31.0	2.56±0.08
Cystine	0.32	33.0	2.74±0.16
Cystine	0.40	30.8	2.62±0.07
Cystine	0.48	31.7	2.71±0.09
Methionine	0.24 (0.19*)	30.7	2.57±0.09
Methionine	0.32 (0.26*)	29.8	2.55±0.11
Methionine	0.40 (0.32*)	35.5	2.77±0.10
Methionine	0.48 (0.39*)	32.0	2.70±0.07

* Equivalent to these percentages of cystine.
† Standard deviation of means.

Table 1 shows the effect of adding cystine or methionine to such a diet containing 10% soybean protein. It is quite clear that both of these S-containing amino acids improve the nutritive value of the ration ‡ for growth as determined by the amount of gain and by the protein efficiency. The improvement increases with the quantity of cystine (or its molar equivalent of methionine) up to 0.3%-0.4% of the protein.

Table 2 shows the combined effects of supplementing with the mixed sulfur amino acids (equimolar mixture of cystine and methionine) and with lysine on the growth of rats. As in the previous experiment the maximum gain was achieved when the diet was supplemented with sulfur amino acids at 0.4 per cent of protein. The addition of lysine, alone or when combined with the S-amino acids, did not improve significantly the rate of growth or the protein efficiency of the diet.

Table 3 shows the results of feeding the S-amino acids and lysine over a greater range than employed previously. This experiment again confirmed the previous results that the addition of lysine was without benefit,§ and that a maximum response was obtained when 0.3% of S-amino acids were added to the soy food protein. At relatively high levels of cystine and methionine supplementation there is some indication that the inclusion of lysine further stimulated the rate of growth. It is not known from these data whether this effect of lysine at relatively high levels of supplementation with the S-amino acids is specific for lysine or simply the result of adding more nitrogen to a nitrogen deficient regimen. However, if it is assumed that the effect is due to lysine, then we have another example of the importance of furnishing the organ-

‡ Mull-Soy contains approximately 5.0 gm. of lysine, 2.3 gm. of cystine, and 1.5 gm. of methionine per 16.0 gm. of nitrogen.

§ It has been suggested that additional lysine, equal to 2.9% of the protein content, will improve the nutritive value of cow's milk. This recommendation was made even though milk proteins contain more than 8% lysine.

TABLE 2.—*Results of Adding Various Levels of Lysine and of Sulfur Amino Acids (Equimolar Cystine and Methionine) to a Soybean Diet Fed to Rats*

Average Gain in Weight (Grams) in Two Weeks

Lysine as % of Protein	Sulfur Amino Acids as % of Protein 0.0	0.24	0.32	0.40	0.48
0.0	19.5	28.8	27.7	33.5	35.5
0.80	21.5	26.0	29.7	32.3	32.2
1.6	----	----	19.2	----	----

Protein Efficiency for Two Weeks

Lysine as % of Protein	Sulfur Amino Acids as % of Protein 0.0	0.24	0.32	0.40	0.48
0.0	1.97±0.16*	2.47±0.04	2.43±0.11	2.68±0.13	2.83±0.09
0.80	2.06±0.14	2.31±0.13	2.51±0.06	2.66±0.08	2.65±0.09
1.6	----	----	1.91	----	----

* Standard deviation of means

TABLE 3.—*Results of Adding Increased Levels of Lysine and of Sulfur Amino Acids (Equimolar Cystine and Methionine) to a Soybean Diet Fed to Rats*

Average Gain in Weight (Grams) in Two Weeks

Lysine as % of Protein	Sulfur Amino Acids as % of Protein 0.0	0.16	0.32	0.64
0.0	16.3	22.3	28.8	25.0
0.24	17.5	19.8	28.3	26.8
0.48	17.0	18.7	27.5	29.0
0.95	16.8	18.2	27.5	27.5
1.9	17.7	22.3	24.8	30.0

Protein Efficiency for Two Weeks

Lysine as % of Protein	Sulfur Amino Acids as % of Protein 0.0	0.16	0.32	0.64
0.0	1.93±0.23*	2.28±0.08	2.60±0.08	2.35±0.07
0.24	1.94±0.13	2.14±0.09	2.56±0.06	2.45±0.08
0.48	1.94±0.15	2.03±0.05	2.50±0.10	2.50±0.09
0.95	1.79±0.12	2.14±0.14	2.49±0.08	2.60±0.12
1.9	1.90±0.14	2.22±0.08	2.34±0.12	2.70±0.09

* Standard deviation of means.

ism with a balanced supply of amino acids. A review of the literature on the effects of unbalancing food proteins by the addition of excessive quantities of an amino acid as well as rebalancing the pattern by the further addition of one or more amino acids is presented by Elvehjem and Krehl [6] and Harper, Benton, and Elvehjem.[7]

Comment

It is now generally accepted that, wherever possible, the pattern of amino acids to be furnished the animal, especially the young rapidly growing animal, should be as near as possible to that required for the formation of new tissue (growth) and for replacing the constant wear and tear of the tissues already formed.‖ During the last 25 years a fairly accurate estimate of the essential amino acid needs of man and other animals has been obtained by three methods: amino acid analyses of optimal diets, amino acid analyses of the carcass at various ages, and feeding experiments.¶

Some of this information is summarized in Table 4. The data in Table 4 have been calculated using tryptophan as unity in order to facilitate comparison. It is obvious that this procedure may exaggerate the errors in the determination of the other values by the error of the requirements (or analyses) for tryptophan. However, inspection of the results in this table shows that the pattern of essential amino acids required by man, rats, pigs, and poultry is remarkably similar. Several points which emerge from a consideration of these data are the following: (*a*) the requirements for

‖ References 1-3, 6, and 7.

¶ References 8-10.

TABLE 4.—*Comparison of the Amino Acid Requirements of Various Animals and the Amino Acid Composition of the Proteins of Cow's Milk, Breast Milk, and Mull-Soy*

	Tryptophan Calculated as Unity										
	Rat						Human		Proteins		
	Adult Maintenance	Adult Repletion	Young	Chick	Turkey Poult	Pig Young	Adult Men	Infant*	Milks		
									Cow	Breast	Mull-Soy
Arg.	0.0	1.5	1.0	6.0	6.2	1.5	0				
His.	1.1	1.5	2.0	1.5		<2.0	0				
Lys.	2.0	3.7	5.0	4.5	5.8	5.5	3.2	3.0	5.6	4.2	3.9
Tyr.	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Phe.	2.2	3.3		4.5		<3.5		3.0†			
Phe. + Tyr.			4.5				4.4		7.7	6.4	7.7
Met.	3.0	2.8	2.0	2.3							
Met. + Cys.			4.0	3.6	3.5	4.0	3.6–4.4		2.8	2.1–3.8	2.9
Thr.	2.8	3.2	2.5	3.0		3.0	2.0	2.0	3.1	2.7	3.7
Leu.	2.8	5.2	4.0	7.0		6.0	4.4		7.3	6.0	5.6
Iso.	5.4	4.3	2.5	3.0	3.1	3.0	2.8		5.0	4.5	3.4
Val.	3.7	3.6	3.5	4.0		3.0	3.2		4.7	5.8	3.3
Gly.	0.0	0.0		7.5	3.8		0.0				

* Data from 11, 12, 13.
† Ample tyrosine included in the diet.
< less than.

lysine with respect to tryptophan is highest in the most rapidly growing animals (This is not surprising when it is recalled that the lysine: tryptophan ratio in muscle is approximately seven); (*b*) there is a decrease in the lysine: tryptophan ratio as the metabolism is changed from rapid growth to adult maintenance in the rat, and (*c*) although the human infant requires approximately eight times as much of each essential amino acid per kilogram of body weight per day as the adult; the ratios of the essential amino acids found by Rose # on adult men (maintenance) and by Holt * on young infants of both sexes are identical.†

The analytical values in Table 4 also show that the proteins of cow's milk, breast milk, and Mull-Soy ‡ contain satisfactory amino acid patterns for the human infant.§ The S-amino acids, and not lysine, appear to be the limiting factor. This is in agreement with the experimental results obtained in the rat studies and contraindicates the supplementation with lysine of milk or soy formulas for infant feeding.

Summary

The addition of L-lysine to a soybean protein diet did not improve the nutritive value of the soy proteins as measured by the rate of growth of young rats. This was true when the lysine was added to the soy protein diet alone or combined with additions of cystine and methionine.

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† The value for the phenylalanine requirement of the infant is probably low because Holt included tyrosine in the diet. Rose has shown that tyrosine will spare large quantities of phenylalanine in the diets of adult men.

‡ References 5 and 15.

§ The impression that the relative requirements for the S-amino acids is smaller for humans than for other animals (rats, fowl) requires confirmation by more modern techniques.

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Atresia of the Foramina of Luschka and Magendie

A Cause of Obstructive Internal Hydrocephalus

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The commonest causes of noncommunicating hydrocephalus in infancy are developmental obstructions at the aqueduct of Sylvius or in the region of the foramina of Luschka and Magendie. Malformation of the aqueduct is most frequently observed, but atresia of the foramina of Luschka and Magendie or functional blockage secondary to an Arnold-Chiari malformation are not uncommon.

Embryologically, the foramen of Magendie is usually formed by the fourth month of fetal life. At this stage of development the cerebellum is dumbbell-shaped with an underdeveloped vermis in the midline connecting two primitive cerebellar hemispheres. Since fluid has already started to form within the cerebral vesicles, the failure of normal formation of the posterior foramina leads to fluid accumulation in the fourth ventricle, inhibiting further development of the cerebellum. As the posterior fossa is thus enlarged because of the cystic dilatation of the fourth ventricle, the developing occipital lobes of the cerebrum cannot push the torcula and lateral sinuses down from their fetal position on the parietal bones as is normally the case.[1] The failure of the normal regressive changes which form the foramina in the posterior medullary velum is therefore the primary lesion by which the patient's clinical and pathologic findings may be explained.

The earliest clinical description of this condition was made by Salter[2] in 1852, three years before the discovery of the lateral foramina by Luschka and before the existence of the foramen of Magendie had been generally accepted. Salter reported a 44-year-old epileptic patient who had never walked and was mentally retarded. At postmortem examination the circumference of this patient's head was 28 in. and the ventricular system contained 6 pints of fluid. The left cerebellar hemisphere and vermis were absent and replaced by a collection of fluid. Although the author did not venture a possible etiology, it seems likely that this represented a case of atresia of the foramina of Luschka and Magendie.

In 1911, Trevor and Rolleston[3] reported the case of a 12-day-old infant who at autopsy had a large cystic cavity in the posterior fossa with a greatly dilated ventricular system. In 1914, Dandy and Blackfan[4] mentioned a patient of this type to exemplify the production of hydrocephalus by posterior fossa obstruction. Priestley,[5] in 1920, presented a case report of a 4-month-old hydrocephalic infant who showed absence of the cerebellum and a cystic accumulation of fluid in the posterior fossa.

The etiology and treatment of this condition were discussed by Dandy[6] in 1921. He described seven cases; three followed meningitis and four were congenital. He stated that the hydrocephalic infant had no distinctive features which might lead to a

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Previously Reported Cases of Surgical Treatment of Atresia of the Foramina of Luschka and Magendie

Author	Year	Age, Yr.	Operation	Result
Dandy[6]	1921	3/12	Ventricular tap	Died
		19	Excision of membrane	Doing well one month postoperatively
		—	Excision of membrane	No follow-up
Scarff[19]	1933	1 4/12	Evacuation of cyst	Recovered
Sahs[14]	1941	16	Posterior fossa exploration	Died
Cohen[15]	1942	13	Excision of membrane	Doing well 15 months later
Taggart & Walker[11]	1942	5½	Fourth ventricle opened into the cisterna magna	Died postoperatively
		1½	Third ventriculostomy	Died postoperatively
		10/12	Air study	Died
Walker[20]	1944	20	Excision of membrane	Doing well one year later
Coleman & Troland[17]	1948	1 2/12	Excision of membrane	Improved one year later
		17	Excision of membrane	Doing well on discharge from hospital
Benda[13]	1954	1/12	Choroid plexus cauterized	Died three months later
Maloney[16]	1954	13	Excision of membrane and cut window in tentorium	Well four years later
Schreiber & Reye[18]	1955	7/12	Lumbar subarachnoid-ureteral shunt	Died one month later
		6/12	Excision of cyst wall	Died postoperatively
			Ventriculogram and pneumoencephalogram	Died postoperatively
		7/12	Excision of membrane	Died four weeks later
		3	Bur holes	Died 12 days later
		Infant	Excision of membrane	Well on discharge from hospital
Matson[21]	1956	8 patients less than 6/12	All had excision of cyst wall	One died two months postoperatively Four needed subsequent lumbar-ureteral shunt Three doing well

specific clinical diagnosis, but rather that this must be made on the basis of special studies. He suggested that a phenolsulfonphthalein dye test be done first, and if the hydrocephalus was found to be noncommunicating, ventriculography should be performed to ascertain the level of obstruction. In his series three patients had surgical procedures. A 3-month-old infant had a ventricular tap and died shortly thereafter. Two older patients had excision of the obstructing membrane, and, although the length of the follow-up period was unsatisfactory, they seemed to be improved after surgery.

Since these early reports other cases have been published * and attempts at surgical correction have been more numerous. The results of these therapeutic efforts have been summarized in the Table.

Report of Cases

CASE 1.—A 5-year-old girl was admitted because of headaches and vomiting of six weeks' duration. The onset of the illness was abrupt—the child was awakened from sleep by a severe headache followed by nausea and vomiting. She became progressively worse and was admitted to a local hospital. A lumbar puncture done at that time was said to have been normal. Twelve days later she was seen in the Outpatient Department of the North Carolina Baptist Hospital and she showed no focal neurologic signs and had no clinical evidence of increased intracranial pressure. Lumbar puncture showed a cerebrospinal fluid pressure of 200 mm. of water, five mononuclear cells per cubic millimeter, and a protein of 35 mg. per 100 cc. The child was sent home where she had less trouble with vomiting and her headache subsided. She apparently was progressing satisfactorily until the morning of admission when she had a generalized convulsive seizure followed by aphasia, severe headache, and vomiting.

Physical Examination.—She had 3 diopters of papilledema bilaterally. The pupils were equal and reacted normally. There was weakness of the external rectus muscles bilaterally. Peripheral reflex activity was normal and no motor or sensory disturbance was noted. She held her head to the side, but there was no nuchal rigidity.

Laboratory Findings.—Roentgenograms of the skull revealed no abnormality except for widening of the suture lines and increased digital markings (Fig. 1).

Course.—The child appeared to be restless and uncomfortable. She took small amounts of fluids

* References 7-10.

Fig. 1 (Case 1).—Plain roentgenogram showing relatively normal shape of head and signs of increased intracranial pressure.

and had episodic vomiting throughout the day. The day following admission she seemed somewhat worse, and it was planned to proceed with ventriculography and exploration, but that evening she suddenly became unresponsive and respirations ceased. A ventricular tap was done on the ward, but her heart had stopped before this was completed.

Pathology.—The most significant finding at autopsy was a cystic dilatation of the fourth ventricle. The thin membrane bounding this area

Fig. 2 (Case 1).—Pathologic specimen demonstrating the arachnoid membrane and the greatly dilated fourth ventricle. Brain stem turned ventrally to give view of fourth ventricle. Note attachment of membrane over wide surface; cerebellar hemispheres widely separated.

posteriorly was ruptured during removal of the brain, but it was estimated that the cavity was at least 5 cm. in diameter (Fig. 2). The cerebellum was compressed, but the vermis was intact; the hemispheres were gray-tan in color and unusually smooth. The aqueduct of Sylvius was dilated two to three times normal size. After formaldehyde solution (Formalin) fixation of the brain, coronal sections were made which showed no remarkable enlargement of the third or lateral ventricles. The lateral foramina of the fourth ventricle were absent, and there was no communication between the fourth ventricle and the pontine cistern. The presence of the midline foramen was uncertain because of distortion of the specimen during removal. There was no gross or microscopic evidence of recent or old inflammation in the region of the fourth ventricle. It was concluded that the cystic dilatation of the fourth ventricle was on the basis of non-inflammatory closure of the foramina of Luschka and Magendie, but the absence of gross dilatation of the third and lateral ventricles suggested that this closure only recently had caused complete obstruction to the flow of cerebrospinal fluid.

Case 2.—A 4-month-old child was admitted because of an enlarging head which was noted first at the age of 6 weeks. He had had no trouble with feedings, seemed alert, and was able to follow objects with his eyes. When first examined at the age of 3 months the circumference of his head was 49 cm.

Physical Examination.—On admission one month later his head showed a circumference of 52.5 cm. and chest 36.5 cm. The anterior fontanel was enlarged, bulging, and tense. The pupils reacted to light well, and the optic fundi were normal. Posteriorly the head transilluminated light easily (Fig. 3) in a triangular pattern, the upper margin being limited by the high attachment of the tentorium. Except for this transillumination of light, the infant showed the typical picture of communicating hydrocephalus.

Laboratory Findings.—The intraventricular cerebrospinal fluid pressure was 300 mm. of water. There were three monocytes per cubic millimeter and a protein content of 54 mg. per 100 cc. The cerebrospinal fluid had a protein content of 68 mg. per 100 cc. Neutral phenolsulfonphthalein injected into the right lateral ventricle passed into the left ventricle and posterior fossa almost immediately but was not recovered in the lumbar region. Ventriculography was done using 30 cc. of air, and the ventricular system was found to be dilated throughout, with an enlarged posterior fossa. The cortex was about 1.0 cm. in thickness. A small extension of air in the posterior fossa was found to protrude down to the level of C-1, but not beyond (Fig. 4).

Fig. 3 (Case 2).—Head transilluminated by light source from behind. Demonstrates the triangular area of transillumination produced by large posterior fossa filled with cerebrospinal fluid (Compare with Fig. 5).

Fig. 4 (Case 2).—Ventriculogram in the "hanging-head" position showing the fluid level in the posterior fossa and a small extension of air protruding through the foramen magnum.

Course.—On the basis of these findings a posterior fossa exploration was done. The arachnoid membrane was carefully separated from the dura mater and inspected down to its attachment to the brain stem. There was no evidence of a midline foramen. The cerebellum was small with a poorly developed vermis, and the bulk of space in the posterior fossa was taken up by a grossly dilated fourth ventricle (Fig. 5). The thin membrane overlying the fourth ventricle was excised and the wound closed.

Postoperatively the child did well except for a pneumonitis which was controlled with antibiotics. However, after an initial period of a few weeks during which the intracranial pressure was normal, obstructive hydrocephalus developed owing to adhesions in the posterior fossa. Multiple attempts by ventriculoperitoneal shunt procedures were made in order to reduce the pressure. These measures were not successful, and the infant died 7½ months after the initial surgery at the age of 11 months.

Pathology.—Autopsy confirmed the operative findings and showed numerous adhesions about the foramen magnum. There was also herniation of an accessory lobe of the liver through the foramen of Morgagni in the diaphragm.

CASE 3.—A 14-month-old girl was admitted because of vomiting, lethargy, and enlargement of her head. Her motor development had been slow, and she had been noted to have jerking movements of her eyes since 4 months of age. When she was 8 months old she had a 3-day period of vomiting which subsided spontaneously. One month before admission she began to have periodic episodes of vomiting. During the week before admission the parents had noted that the child's head was growing larger.

Physical Examination.—The circumference of her head was 53 cm. and chest 45 cm. The anterior fontanel was 4 cm. in diameter and was tense and bulging. There was early papilledema bilaterally. There was weakness of the right external rectus muscle, and the pupils were dilated and did not react to light. Reflexes were equal and hyperactive bilaterally.

Laboratory Findings.—Roentgenograms showed the cranial sutures to be separated. Head shape was normal. A phenolsulfonphthalein dye test demonstrated lack of communication between the lateral ventricles and the lumbar subarachnoid space. The intraventricular cerebrospinal fluid pressure was 440 mm. of water. Ventriculogram showed dilatation of the ventricular system including the third and fourth ventricles.

Course.—Posterior fossa exploration was done and when the dura mater was opened a large cystic cavity was found surrounded by arachnoid membrane. The cerebellum was hypoplastic, and the brain stem was abnormally wide and flattened. The aqueduct of Sylvius was dilated. The arachnoid membrane was followed down to its attachment and found to extend by means of a finger-like projection into the upper cervical spine and fuse with the meninges in this region. A catheter could not be passed into the upper cervical region from the posterior fossa for more than 1 cm., but after a defect was made in the membrane it could be passed into the cervical subarachnoid space without difficulty. A shunt was then placed between the right lateral ventricle and the cervical subarachnoid space.

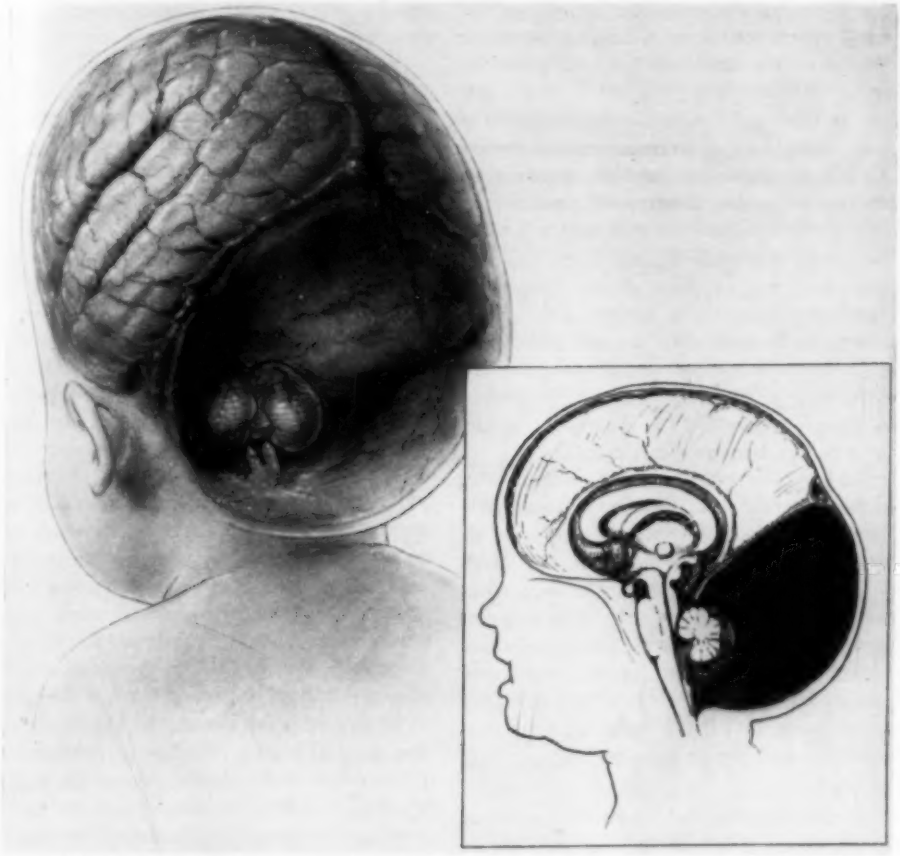

Fig. 5 (Case 2).—Appearance of cerebellum and posterior fossa as seen at operation. The cerebellum, well developed in this patient, lies in the depths of a large fluid-filled cavity.

Postoperatively the child did well and the fontanel remained soft for three days. On the fourth postoperative day she began to develop increasing rigidity and Cheyne-Stokes respirations. Her right eye deviated down and in and the left eye was turned up and out, suggesting a right middle cerebellar peduncle syndrome. She was placed on ventricular drainage, but despite this her vital signs became progressively more unstable and she died on the eighth postoperative day.

Pathology.—At autopsy a blood clot was found in the posterior fossa. The cerebellar hemispheres measured 3 by 4 cm. The vermis of the cerebellum was absent. There were areas of focal degeneration and hemorrhage in the brain stem.

Comment

From a review of the literature as well as observation of patients with occlusion of the foramina of Luschka and Magendie it seems evident that, although more frequent in the first two years of life, this condition may become symptomatic at any time during childhood. The length of the latent period before symptoms appear depends on the degree of obstruction which is present. In general, the presence of symptoms in early infancy represents complete atresia of all foramina, but in later childhood such is not the case. Because of these variations in the degree of obstruction, the clinical picture and diagnostic studies may show certain differences.

Children with complete congenital atresia of the foramina of Luschka and Magendie are noted to have hydrocephalus within the

first three months of life. They show the more typical picture of a bulging posterior portion of the skull which transilluminates light. The posterior fontanel is large and late in closing. Phenolsulfonphthalein dye tests show lack of communication between the lateral ventricles and the lumbar subarachnoid space. Roentgenograms aid in making the diagnosis because on plain films the impression made by the lateral sinuses sometimes can be seen in an abnormally elevated position of the parietal bones, indicating the lack of their normal downward migration. Sinograms will confirm this by more clearly outlining the lateral sinuses. Ventriculography is of diagnostic value, since in the hanging-head position (as described by Matson) [11] there is a fluid level in the posterior fossa showing a large cystic space and frequently a small projection of air extending down to the C-1—C-2 level, but not beyond. Pathologically these children have enlargement of the ventricular system and malformation of the cerebellum with a small or absent vermis and hypoplasia of the hemispheres. There also may be obliteration of the basal cisterns and cervical subarachnoid space by congenital adhesions.

In those children who have delayed onset of symptoms the head may or may not be enlarged and usually is of normal shape. This depends on the duration of total obstruction and the stage of cranial development when occlusion of the foramina occurs. These patients may have variable cerebellar signs for months or even years before acute pressure supervenes. Occasionally the occurrence of complete occlusion seems to coincide with an episode of straining.

Roentgenograms may reveal the lateral sinus to be in normal position, but ventriculograms show the same findings as in the earlier group. The small projection of air into the upper cervical region is an important point which differentiates this type of occlusion from one due to postinflammatory adhesions or tumor, since in these cases the fourth ventricle has a blunt and rounded inferior corner which is wholly within the posterior fossa.

Pathologically this group of patients is interesting. The foramen of Magendie is always absent, and there is frequently a recess in the midline in the roof of the fourth ventricle which projects down into the upper cervical region. The foramina of Luschka are usually absent but on occasion may be demonstrably patent at operation or autopsy.† This is the case only with the chronic syndromes and has not been reported in those patients who have acute onset of pressure symptoms. There is no clinical or pathologic evidence of inflammation, and therefore it is assumed that the condition is congenital. The pathogenesis of this delayed syndrome is in doubt. It might be postulated that a transient increase in intracranial pressure could cause a tuft of choroid plexus to form a ball-valve obstruction of the single patent foramen of Luschka, the other foramina being congenitally occluded. This might remain obstructed by the increasing intracranial pressure. It has been found that the foramen of Magendie is not present in 1% of otherwise normal human brains,[13] and that there is some variability in the size of the foramina of Luschka; therefore, it seems likely that on occasion the situation described above might exist. In these cases of late onset the cerebellum may be small and the vermis hypoplastic, elevated, and pushed forward. The subarachnoid pathways may show some adhesions, but in the older children the pathways usually are well formed.

Although theoretically this is an easily remediable lesion, surgical treatment is not universally successful, especially in the younger age groups. In infants removal of the cyst membrane frequently does not permanently relieve the intracranial pressure, presumably because the congenital adhesions of the subarachnoid pathways have left them underdeveloped and adequate absorption of cerebrospinal fluid does not occur. In these children if pressure is not satisfactorily controlled by relieving the ob-

† References 10 and 12.

struction in the posterior fossa, it is usually found that the obstructive hydrocephalus has been converted into a communicating hydrocephalus. Further surgery may be necessary to shunt the cerebrospinal fluid either into the peritoneal cavity or the ureter. In older age groups simple removal of the arachnoid membrane over the dilated fourth ventricle is likely to be curative.

Conclusions

The literature relating to congenital atresia of the foramina of Luschka and Magendie and its treatment has been reviewed. Three cases are presented to illustrate some of the common clinical and laboratory findings. The cases of posterior foraminal occlusion are divided into two groups with differing symptomatology, deriving from the fact that the obstruction may be congenitally either complete or incomplete. The diagnosis should be suspected in any infant with an enlarged head and may be confirmed by transillumination of light through the congenitally enlarged posterior fossa.

Surgical therapy consists in relieving the obstruction in the posterior fossa. In small infants in whom the subarachnoid pathways may not have been properly formed, a lumbar subarachnoid-peritoneal or ureteral shunt may be necessary to reduce intracranial pressure.

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Congenital Defect of the Bony Orbit and Pulsating Exophthalmos

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Defects of the bony orbit are rare in childhood; therefore, when they are encountered in association with clinical signs and symptoms or as an incidental observation, various diagnostic possibilities arise. This consideration is not given to certain specific entities capable of being suspected on clinical grounds. Experiences with two instances of this rare anomaly have prompted us to report the problems presented and their management.

The embryology and anatomy of the orbit are available in standard textbooks * and will not be discussed here. However, it is proper to note that both membranous bone and cartilaginous bone enter into the formation of the orbit, and that several natural apertures provide communication with the cranial cavity.

Report of Cases

CASE 1.—A white boy was born on April 5, 1944. He was the first child of young healthy parents. The pregnancy and delivery were not unusual; no disease during pregnancy was recorded. No history of familial disease was present; in particular, none of the parents or grandparents were known to have neurofibromatosis.

An enlargement in the region of the right temple was first noted by the father when the baby was 2 months of age. A physician was consulted at the time, and the parents were reassured. At 11 months of age someone again noticed this bulge, and the patient was admitted on March 19, 1945, to the Children's Hospital of Cincinnati for observation. The mother stated that the size of the mass had been stationary.

On physical examination the patient was well nourished. His weight was 9200 gm., and his head circumference was 45 cm. At the site of the right anterolateral fontanelle, a swelling of about 3.5×4.5 cm. was present (Fig. 1). The swelling was firm and nodular to touch and raised ½ cm. above the remaining bony level. The skin over the mass was freely movable. A pulsating exophthalmos was present on the right side, the proptosis measuring 0.5 cm. External ocular movements were normal in all directions.

Fig. 1.—Case 1 at 11 months of age. The right eye and its upper lid are more prominent than the left and the right frontotemporal region is "swollen."

The roentgenograms (Figs. 2 and 3) demon-

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* References 1-4.

Fig. 2.—Case 1 at 2½ years. Frontal projection of skull. The right orbit is enlarged, and the right side of the skull is larger than the left. The landmarks of the bony orbit on the right have disappeared and neither orbital fissure can be recognized. The defect in the region of the posterolateral fontanel is projected through the clear orbit.

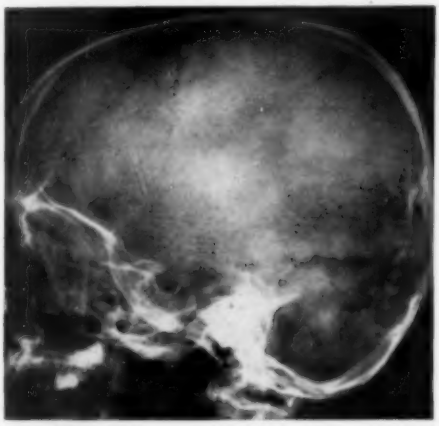

Fig. 3.—Case 1 at 2½ years. The partial absence and thinning of the roof of the right orbit is clearly shown, as well as the enlargement, downward and forward, of the floor of the middle fossa.

strated an asymmetrical skull with disproportionate enlargement of the right side of the cranial vault. The middle fossa was markedly enlarged on this side. These abnormalities were associated with presence of large defects of the frontal, sphenoidal, temporal, parietal, and occipital bones in the region of the right anterolateral and posterolateral fontanelles. The defect had irregular margins, but there was no sclerosis and no evidence of proliferative reaction at the margins. The anterior defect measured 3×3.5 cm. in its greatest diameters. The posterior defect measured 2.5×3 cm. in its greatest diameters. The anterior portion of the parietal bone near the region of the pterion bulged outward and was thinned. The bony orbit was enlarged on the right side; the roof and lateral walls were almost completely absent. The medial wall as well as the pterygoid plates were displaced toward the left. The floor of the nose was depressed. The examination of the long bones was negative for any abnormality.

On April 4, 1945, an exploratory operation was performed over the temporal mass. At the site of the mass, what appeared to be thickened dura occupied the skull defect and covered the brain. A specimen from the outer layer of this membrane was taken for biopsy. The bone just superior to the skull defect appeared to be normal but very thin. No soft-tissue tumor or bone tumor was seen in the exposed area. The orbit was not explored at this operation. The biopsy material was reported to be normal dura.

After discharge from the Children's Hospital, the patient received four x-ray treatments to the skull in another city.

The condition continued to progress slowly and radiographic examinatons of the skull in April, 1947, showed further increase in size of the orbit.

Because of the increase in the size of the mass and exophthalmos, the patient was readmitted in 1951 at 7 years of age for further studies. He also had had occasional headaches and had considerable visual difficulty with the right eye, because of loss of muscular control.

The boy was normal in all respects except for the right eye and the skull. No skin lesions of the type associated with neurofibromatosis were found. Swelling in the right frontotemporoparietal region (Fig 4), pulsating exophthalmos, and medial deviation of the right globe were the outstanding findings. The soft protruding swelling was 2.5 cm. in diameter and was pulsating. Ptosis of the right upper lid was also present. The right external auditory canal was distorted. No visual abnormalities were observed in either eye, and the fundi were normal.

Pneumoencephalographic examination demonstrated the right lateral ventricle to be larger than the left; no porencephalic cavity was observed. The subarachnoid air extended into the orbital defect (Fig. 5). Cerebral angiogram revealed no disturbance of the vascular structure on the right side. However, the carotid siphon was displaced somewhat toward or into the posterior aspect of the orbit, and extension of cerebral substance into the right orbit was suggested.

On June 19, 1951, a right frontotemporal craniotomy was done. No tumor was present in or about the brain, and the orbit was found also to

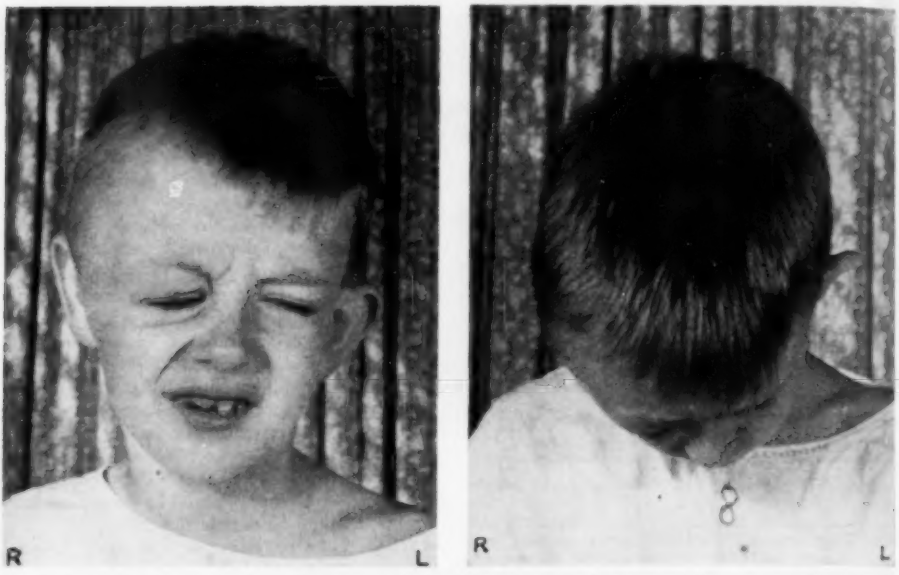

Fig. 4.—Case 1 at 7 years. *A*, the right palpebral fissure is displaced downward and the frontotemporal bulge is grossly disfiguring. *B*, the bulge of the right frontotemporal region and the anterior displacement of the external orbital soft tissues are obvious.

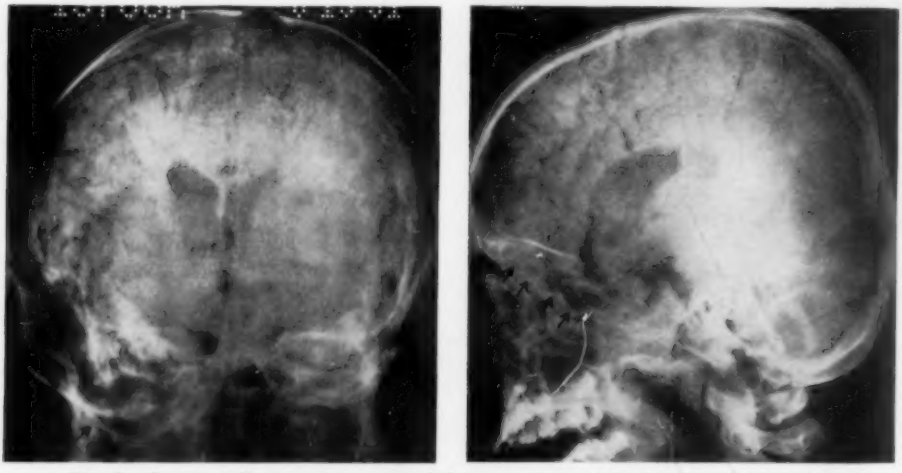

Fig. 5.—Case 1 at 7 years, pneumoencephalogram. *A*, the right lateral ventricle is dilated but no displacement is present. Note the displacement of the floor of the middle fossa (arrows). *B*, brow up, horizontal beam examination fails to show temporal horn, but subarachnoid air on the right side (arrows) extends into the orbit.

be clear of tumor. The orbital roof was absent as was a major portion of the greater wing of the sphenoid bone. What appeared to be the sphenoidal ridge was extremely high and far anterior on this side. The middle fossa was markedly enlarged. Dura was present at the site of the defect. Dural biopsies were taken, two from the area of the cerebral hemisphere and another from the orbit. The patient made a satisfactory recovery from this exploratory operation. Microscopic examination of the biopsy specimens demonstrated fibrosis and very slight chronic inflammation. No tumor cells were seen.

The patient was discharged. The mass continued

to increase in size, and the exophthalmos also progressed. On July 7, 1954, the patient underwent another operation. Dr. Andrew M. Moore, of Lexington, Ky., performed this operation, and we are indebted to him for the follow-up report. An incision was made over the mass. A soft subcutaneous tumor with the appearance of edematous tissue was removed from the temporofrontal and periorbital regions. The tumor measured 6×10×12 cm. Microscopic examination disclosed characteristic neurofibromatosis. Reexamination of the material removed in 1951 permitted a diagnosis of neurofibromatosis from this material as well.

Our last communication from the parents was nine months after the operation. Marked improvement in physical appearance of the face was reported, and the patient's emotional state was greatly benefited. The strabismus was still present.

CASE 2.—A white boy now 4 years old, was born on Dec. 11, 1950, to young, healthy parents. Pregnancy was uneventful. The baby was born by Caesarian section. Birth weight was 3500 gm. Except for diabetes mellitus in the maternal grandmother, no other important familial diseases were reported. An older brother, born in 1949, had been in good health. The brother had been in an automobile accident, and the radiographs of his skull were reviewed and showed no abnormalities. Radiographic examination of the mother's skull demonstrated no abnormalities.

The patient was admitted to the Children's Hospital of Cincinnati on Jan. 5, 1955, for evaluation of an abnormality of the skull detected in films taken at another hospital. The initial x-ray examination was undertaken because the patient's mother had been concerned about many minor or moderately severe head blows this child had received in the course of play and wandering about the house. There had been no history of unconsciousness, convulsions, or vomiting.

Physical examination, in particular examination of the eyes and central nervous system, was negative for any abnormality except for a very questionable Babinski's sign. Radiographic examination demonstrated the presence of a large defect in the posterior aspect of the right bony orbit. The initial impression was an enlargement of the superior and inferior orbital fissures, making them one; this resulted from the absence of part of the greater wing of the sphenoid bone (Fig. 6). No other abnormalities were recognized.

Because of the unexplained presence of this defect, the patient was admitted for a medical work-up, electroencephalogram, pneumoencephalogram, cerebral angiogram, and possibly even an exploration. The possibility of congenital malformation was not entertained in this patient until after admission. In the absence of any disturbance related to the abnormality and with the recognition that the optic foramen was normal, no further studies were recommended or undertaken. The patient will be examined at regular intervals. The development of symptoms or signs of progression will demand revaluation.

Fig. 6.—Case 2. Defect in bony orbit on right uniting the superior and inferior orbital fissures. Incidental observation in asymptomatic child without pulsating exophthalmos. This is considered an early stage or lesser degree of the malformation which is so obvious in Case 1.

Comment

Nature of Defect.—Gross pathologic reports from surgical exploration or autopsy findings and microscopic reports similar to the one we have for our first patient are frequent among a number of operated cases and patients seen at autopsy. These indicate that the condition is one of encephalocele or cerebral hernia through congenital defect in the bony orbit. The defects are of two types, anterior and posterior.[5] The anterior type is commonest and is located between the frontal bone, lacrimal bone, cribriform plate, and nasal process of the maxilla. Sometimes the herniation is visible at the base of the nose. In the posterior type the opening may be a natural opening, normal in size or enlarged, such as the posterior

ethmoid foramen, the superior orbital fissure as in Case 2, or the optic foramen.

Herniation of the cranial contents through a defect of bony orbit has been recognized at least since 1903. In the discussion of Rockliffe's and Parsons' report of a case of "Pulsating Exophthalmos (Congenital)," the possibility of meningocele was raised. The afflicted child died after surgery. In this patient the entire orbital plate of the frontal bone, the lesser and greater wings of the sphenoid bone, and the orbital wall of the ethmoid bone were missing. The pathologic diagnosis was plexiform neuroma of the orbit. Since then, many reports of the anterior type and a limited number of the posterior type of bony defect have appeared in the literature.†

Strandberg [16] reviewed the literature of 1841 to 1948 and reported 31 cases of the posterior type and added one of his own. Since 1948, other cases of this type have been published.‡ LeWald [5] reported four cases of congenital absence of the superior orbital wall, and in one of these Dandy [17] made a new orbital wall by means of a bone transplant from the skull. King [18] reported traumatic encephalocele of the orbit. The most recent report by Bruwer and Kierland [24] adds six new cases, one almost identical with our first patient.

The posterior orbital cephalocele of the type herein described falls into the classification of "basal cephaloceles" an uncommon form of craniocerebral malformation. Strandberg [16] cites Reale's review of reported cases of cephalocele with the following distribution: occipital, 86; frontal, 33; parietal, 12; lateral, 8, and basal, 1. In the case of Robertson [15] the posterior part of the orbital plate of the frontal bone, the lesser wing of the sphenoid bone, and the vertically directed orbital part of the greater wing of the sphenoid bone were absent. Cohen [11] reports a patient whose radiograph demonstrated the optic foramen to be larger than on the normal side; it was circular, clear, and did not show erosion. Moore [19] refers to enlargement of the orbit in this type of defect.

Other abnormalities of the skull and eyes may be present in conjunction with the orbital defect. Our first case presents a good example of such abnormalities. The large temporal lobe, the small frontal lobe, and the bony defects of the temporal and parietooccipital regions were significant findings in this patient. In the case reported by Parson and Coats [20] there was a temporal defect and malformation of the eye and brain. Four of the thirty-one cases with posterior orbital defects [16] were associated with microphthalmos and one with a coloboma of the optic nerve. The position of the intracranial vessels may be abnormal as is shown in our angiogram in which there is forward displacement of the carotid siphon. In Strandberg's [16] patient the carotid artery was peculiarly twisted in relation to the dura mater. Dandy [17] found a large extradural vein at operation which he thought had replaced the cavernous sinus; the internal carotid artery also was absent on the affected side.

The herniated brain may be covered by dura or the dura may have been ruptured exposing the brain to the posterior aspect of the eyeball.

Neurofibromatosis and Orbital Defect.—Many cases of neurofibromatosis in conjunction with partial absence of the orbital wall have been recorded in the literature.§ As early as 1902, in the paper of Rockliffe and Parsons [21] the presence of a plexiform neuroma with congenital defect of the orbital wall was suggested. LeWald [5] reported two patients with the same condition. Seaman [9] also reported two cases. Peyton and Simmons [13] collected 20 cases of neurofibromatosis with defects in the orbital wall and studied five of their own. They stressed that spina bifida, hypospadias, glaucoma, and elephantiasis are only a few of the congenital defects seen in conjunction with neurofibromatosis. Of five cases of orbital defect presented by Wheeler [6] one had a

† References 5-7, 9-16, and 24.

‡ References 15-24.

§ References 5, 6, 9, 19, 21, and 24.

plexiform neurofibroma. Five of the six cases of Bruwer and Kierland had evidence of cutaneous neurofibromatosis [24]; a neurofibroma of the orbit was present in one.

It is inconceivable that a tumor mass of the size described at the third operation of our first patient could have been missed during the first two operations, if this were the cause of the bony defect. The bony defect has probably been present since early fetal life. The subcutaneous neurofibromatosis of the right frontotemporal region probably had been present too, at or very soon after birth, increasing in size until its removal at 10 years of age. The failure to identify the mass initially repeats the experience in Bruwer and Kierland's Case 1,[24] and suggests that the striking intracranial abnormalities distract the neurosurgeon from the subcutaneous lesions until the latter attain an appreciable size.

Clinical Features.—The presenting signs of congenital orbital defects are temporal and frontal mass and pulsating or nonpulsating exophthalmos. It is very unusual to find orbital defects as an unexpected incidental finding in the routine examination of the skull for ruling out a fracture. Whether or not minor orbital roof defects are being missed is a question to be answered by a careful examination of each skull film, looking particularly for these defects. Variations in size and configuration of the orbital fissures may make interpretation difficult. Serial examinations of suspected cases may reveal progressive changes which permit a diagnosis. Our first patient demonstrated slow progression of signs and symptoms; our second has not been observed long enough to evaluate in this regard. The tumor mass at the temperofrontoparietal region is usually soft, elastic, and may pulsate. Medial displacement of the globe has been seen [16] much less commonly than has downward and lateral deviation; this observation results from the fact that the hernial mass is mostly mesial in location. Edema of the lid and ptosis, as present in Case 1, is a rather common finding. The edema is more in the upper and less in the lower lid. Vision may be disturbed in patients with large lesions because of the mechanical effects of herniation and pulsation. The exophthalmos is unilateral, minimal at first, but slowly progressive. Its pulsation is synchronous with cardiac systole and can be reduced by pressure on the globe, occlusion of carotid arteries [15] and removal of cerebrospinal fluid.[25] No bruit can be heard. The patient is not disturbed by the pulsations.

Radiologic Features.—The lesions are so similar when studied radiographically that the diagnosis may be strongly suggested, and clinical conditions permitting biopsy often may be deferred until it can be combined with definitive surgery. The radiologic features may vary with the degree of involvement and with the age of the patient, increasing with the passage of time; but one feature is common to all cases: a defect in the bony orbit. In the posterior variety, exemplified by our two patients, the apex of the orbit is lacking together with variable contiguous portions of the roof and adjacent walls. The orbit is enlarged on the affected side; in frontal projection usual landmarks are missing. The lesser wing of the sphenoid which appears to extend laterally from the medial wall may be impossible to identify. When the greater wing of the sphenoid is involved, the orbital fissures enlarge and coalesce and ultimately the bottom seems to have fallen out of the orbit. The view through it is usually clear and contrasts with the opposite side. Generally, the optic foramen is not involved.

When the defect is large and cerebral herniation is prominent, the "sphenoid ridge" on the affected side appears to be displaced forward and upward. Actually the "ridge" is the free posterior aspect of the floor of the anterior fossa and is composed largely of orbital plate of the frontal bone. The anterior fossa is thereby diminished in size and the middle fossa relatively increased. An actual increase takes place as well in the middle fossa, the floor of which is observed to bulge forward and downward in both coronal and sagittal pro-

jections. In lateral projections the usual parallelism of the orbital roofs and of the floors of the middle fossa is lost. In fact, with large defects only a single line may be recognized, tracing the contour of the orbital roof on the healthy side. If two lines are present, the one on the affected side may fade out as it courses posteriorly, appearing shorter than its fellow.

Defects may be present in the regions of the anterolateral and posterolateral fontanelles. These may be defects in mineralization recognized only by radiographic examination and feeling quite intact to palpation. The radiolucency and the expansion combine to make indistinct or to make disappear totally the temporal line of the greater wing of the sphenoid.

Pneumoencephalography may demonstrate a normal ventricular system, asymmetry has been observed and results from movement of the cerebral substance into the spaces produced by defects in the bony cranium. The ipsilateral ventricle was dilated in our Case 1. A diagnostic feature of the cerebral herniation is the identification of subarachnoid air extending into the orbit but still conforming to the shape of the invisible dura. This feature is best seen by means of lateral horizontal beam examination in the "brow-up" position. Cerebral angiography demonstrates only spatial alterations of vascular structures conforming to the cerebral displacements.

Differential Diagnosis.—With the radiographic findings and clinical picture in the presence or absence of neurofibromatosis the diagnosis is not difficult. The following are some of the disorders which should be differentiated:

1. Arteriovenous Fistulae: Pulsating exophthalmos may suggest this diagnosis. Martin and Mabon [8] reviewed 812 cases of pulsating exophthalmos and found retrobulbar tumor of soft tissues, bony orbital tumors, vascular lesions, such as varicocele, and arteriovenous fistulae to be the main causes. Arteriovenous fistulae usually occur after trauma or infection. The examiner can hear a bruit, and the patient is aware of the abnormal sound which is disturbing to him. There is usually a significant amount of vasodilatation of the orbital vessels. A bony defect is usually not present.

2. Xanthomatosis: Orbital defects similar to the ones under discussion may be present without any pulsation. The lack of pulsation has been explained by the replacement of bone by xanthomatosis tissue which resists pulsation.[6] The radiographic picture can be confusing. The lack of reaction about these congenital defects and their occurrence in both membranous and basal portions of the skull are comparable to that of xanthomatosis. But clinical signs of chronic otitis, diabetes insipidus, etc., are lacking in the congenital defects. The presence of similar defects in both bones also favors the diagnosis of xanthomatosis.

3. Dermoid and Epidermoid Tumors of the Orbit: Pfeiffer [22] in a series of 200 consecutive cases of exophthalmos found these congenital growths to account for 4% of the cases. The dermoids and epidermoids produce characteristic defects in the diploe of the skull or bones of the orbit, expanding the diploic space. They have sharply demarcated margins with increased density of the bone at the margins. These dense borders surround the radiolucent mass. The presence of fat probably accentuates the radiolucency.

4. Surgical Defects: The operative removal of a rather large area of the bony orbit usually does not result in pulsating exophthalmos.[23] This fact can probably be explained by the presence of scar tissue which replaces the destroyed bone and an intact dura. Verbiest [23] reported a patient who developed pulsating exophthalmos after a postoperative meningitis; the exophthalmos subsequently subsided spontaneously.

5. Traumatic Defects: In 2 of 32 cases with posterior orbital defect, exophthalmos developed soon after trauma to the eye.[16] In chronic hydrocephalus increased pressure may result in thinning of the orbital roof and trauma may then cause a communication between the intracranial and the orbital cavities.[23] Proptosis of the globe may occur

some months after trauma and disruption of the dura and the floor of the anterior fossa of the skull.[18] A traumatic defect of the roof of a normal orbit and defect in conjunction with hydrocephalus should not present any diagnostic difficulty.

Conclusion.—We believe our two patients demonstrate congenital defects of the bony orbit with actual or potential herniation of cranial contents into the orbit for the following reasons:

1. Bone erosion from infection or pressure of tumor masses should produce some signs and symptoms of infection or mass lesion. Pulsating exophthalmos in Case 1 is adequately explained by the cerebral protrusion. Moreover, there was no tumor mass in bone or compressing bone from the endocranium; the tumor mass in the orbit may have contributed to the degree of proptosis, but the tumor could not have accounted for a defect bulging toward it. The association of neurofibromatosis is therefore considered only coincidental.

2. Defects of the skull were present in areas other than the orbit in Case 1. Neurofibromatosis masses were not present at least externally, and the pneumoencephalogram would tend to exclude any internal mass.

3. The syndrome of orbital defect and pulsating exophthalmos has been described in the absence of neurofibromatosis.

Summary

Radiographically demonstrable defects of the bony orbit occur in association with exophthalmos which may or may not pulsate. In a significant number of cases neurofibromatosis is present, locally, in or adjacent to the orbit, or elsewhere in the body. The cranial defect is probably an associated malformation. Herniation of the brain occurs into the orbit and is responsible for pulsation when it is present. The condition is therefore properly understood as an intraorbital encephalocele.

Case reports of two children are described. In one, exophthalmos, asymmetry of the skull, and palpebral edema were noted. Exploration at 1 year and again at 7 years of age was unrewarding, but at 10 years of age a large neurofibroma was removed from the orbit and review of biopsy specimens from the second procedure indicated that the lesions were present then. Cosmetic improvement relieved emotional tensions. In the second patient a radiologic diagnosis was made as an incidental result of x-ray examination for minor skull trauma. Initial consideration of more serious destructive lesions almost led to major surgical intervention.

Clinical and radiologic features of the condition are described, and a differential diagnosis is discussed.

Dr. Andrew M. Moore provided the completion of the history of the first patient, and Dr. Lee Rosenberg supplied the radiographs for the second patient.

Dr. Benjamin Landing reviewed the histologic material from the initial biopsy in the first case and concurred in the diagnosis of the tumor removed at the third operation.

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Treatment of Measles Encephalitis with Corticotropin

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It is well known that measles encephalitis is frequently followed by serious neurologic residua and that it is associated with an appreciable case fatality rate, variously estimated between 10% and 30%. In an effort to combat this dread complication of measles, many forms of treatment have been introduced from time to time, only to be discarded as experience has shown them to be without value. Of particular interest was a report [1] recommending the use of gamma globulin. However, in a recent study by Greenberg and co-workers [2] it was shown that gamma globulin has no value in the treatment of measles encephalitis.

The recent studies of Kabat and associates [3] and of Moyer and his co-workers [4] which show that experimental demyelinating encephalomyelitis can be suppressed by pretreatment with either corticotropin or cortisone made it seem worth while to investigate the value of hormonal therapy in human encephalomyelitis. This paper is based on the use of corticotropin (ACTH) in a series of 17 consecutive cases of measles encephalitis which were seen between Jan. 18, 1952, and buly 28, 1955.

Diagnosis

Clinical Aspects.—The patients presented the typical symptoms of acute encephalitis complicating measles, including pronounced changes in the sensorium. Individual patients showed variation in the severity of the disease, but most of them appeared critically ill.

Table 1 shows the sex and age distribution and the salient clinical features in this group of patients. It should be noted that 14 of the patients had convulsions and that 10 were in a state of coma.

Spinal-Fluid Findings.—A spinal tap was done at least once in all but one case. The results of the spinal fluid examinations are shown in Table 2. The fluid was clear in most instances and was frequently under moderately increased pressure. A moderate increase in the number of white cells was the commonest abnormal finding. Two cases had a normal spinal-fluid cell count. The predominating cells were lymphocytes. There was a slight to moderate increase in the protein content in 10 cases. The sugar level was normal or elevated in all instances. Chloride determinations, made in 14 cases, ranged between 685 and 771 mg. per 100 cc. Smears and cultures for micro-organisms were negative in all cases.

Treatment

All the patients in this series were treated with corticotropin. The schedule of treatment is shown in Table 3. The medication was administered either intravenously or intramuscularly. In most instances the initial treatment was given by vein. The daily dose of the hormone varied from 5 to 80 mg., with 25 mg. being the commonest. The duration of the hormonal therapy ranged between 1 and 14 days and was one week or less in the majority of the cases. The total amount of the drug given individual patients varied considerably and ranged

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TABLE 1.—*Salient Clinical Features in Seventeen Cases of Measles Encephalitis*

Case No.	Sex	Age, Yr.	Temperature	Convulsions	Mental State	Meningeal Signs	Cranial Nerve Involvement
1	M	1½	104	+	Coma	–	
2	M	3	104	+	Lethargy	+	Strabismus
3	F	3½	102.4	+	Coma	–	Left facial palsy
4	F	5	103	+	Coma	+	
5	F	5	100.6	+	Delirium	+	
6	M	5	100	+	Coma	+	
7	M	5	102.6	+	Semistupor	+	
8	F	6½	105	+	Semistupor	+	
9	M	7	106	+	Coma	+	
10	M	7	101	+	Delirium; lethargy	+	
11	F	7½	102	+	Lethargy	+	
12	M	8	106	+	Coma	+	Optic neuritis
13	M	8	101	+	Coma	+	
14	F	9	103	–	Clear	–	Right facial and palate palsy
15	F	9	102	–	Coma	+	Oculomotor palsy
16	F	9½	102	–	Coma	+	
17	M	10½	105	+	Coma	+	

from 100 to 320 mg. in most instances. In all but six cases treatment was instituted on the day of onset of the encephalitis. Therapy in the exceptional cases was delayed for three to six days. Additional treatment was of a palliative nature, except for the use of antibiotics in several instances for prophylactic purposes.

Results

Initial Response and Clinical Course.—The initial changes indicative of clinical improvement that followed the hormonal therapy appeared early in the majority of the cases. In 11 patients remission of the fever and a decisive amelioration in the mental state were noted in one to four days. In the remaining six cases these changes were evident in 6 to 13 days. After the initial favorable response, improvement usually progressed satisfactorily, though with varying duration of the different symptoms in individual patients. In several of the cases, however, the clinical course was complicated by certain adverse developments. For instance, the patient in Case 12 had impairment of vision, the patient in Case 15 had difficulty in focusing, the patient in Case 4 lost his power of speech, and the patient in Case 2 had recurrent convulsions. These complications were transitory in nature, except for the persistence of the aphasia in Case 4.

Outcome.—In this series of 17 cases there were no deaths. Fourteen patients were discharged from the hospital without any neurologic or other detectable abnormalities. Three patients showed at the time of discharge residual central nervous system stigmas, which included impairment of

TABLE 2.—*Spinal Fluid Findings in Sixteen Cases of Measles Encephalitis*

Case No.	Cell Count	Protein, Mg/100 Cc.	Sugar, Mg/100 Cc.	Chlorides, Mg/100 Cc.
1	Blood tinged	26	130	728
2	85	58	84	738
3	135	60	98	665
4	120	52	155	740
5	47	102	138	766
6	10	36	78	755
7	103	75	62	722
8	Spinal tap not done			
9	90	100	190	
10	85	36	70	706
11	90	80	80	771
12	5	34	60	768
13	90	86	140	719
14	75	38	89	760
15	2	47	50	
16	40	54	134	733
17	140	26	76	740

vision, loss of speech, euphoria, and mental retardation.

In a follow-up study information was obtained on all but one patient, who could not be located; her status after the original observation which showed her to be in excellent condition, is not known. The results of the study in the remaining 16 patients are presented in Table 4. The shortest follow-up period was seven months, and the longest was three years nine months. For 14 patients the follow-up period was longer than one year. Fifteen of these sixteen patients escaped without any residual symptoms. In one patient there were marked neurologic sequelae.

Comment

The favorable outcome in this series of cases is very impressive. This is noted in the absence of fatalities, in the early improvement in the great majority of the cases, and in the excellent physical and mental condition of all but 1 out of 16 patients on follow-up study. The exception was the patient in Case 4, who showed serious neurological residua.

As previsusly noted, the hormonal therapy was instituted early in the disease in most of the cases in this series. To what extent this was a factor in the favorable outcome is a matter of speculation, particularly since treatment was started on the day of the onset of the encephalitis in the one case with sequelae. It is assumed that severe neurologic residua are related to demyelination, which, as shown by one of us (E. A.) in a previous study,[5] begins to appear on the third day of the disease. Although little

TABLE 3.—*Schedule of Corticotropin Therapy in Seventeen Cases of Measles Encephalitis*

Case No.	Day of Encephalitis Treatment Started	Daily Dose, Mg.	No. of Days Treated	Total Dose, Mg.
1	6	12.5-25	2	37.5
2	1	25	2	50
3	1	25-50	3	100
4	1	25	7	175
5	1	50	5	250
6	5	80	4	320
7	1	25	1	25
8	1	10-50	8	200
9	1	15-25	6	130
10	4	15-25	3	65
11	3	20-25	10	245
12	1	10-25	7	150
13	1	5-20	14	160
14	4	15-25	3	65
15	3	20-25	10	245
16	1	10-25	7	150
17	1	5-20	14	160

TABLE 4.—*Follow-Up Findings in Sixteen Corticotropin-Treated Cases of Measles Encephalitis*

Case No.	Follow-Up Period	Physical and Mental State
1	1 ½ yr.	Normal
2	7 mo.	Normal
3	No follow-up	
4	3 yr. 8 mo.	Mental retardation; impairment of speech
5	1 yr. 7 mo.	Normal
6	1 ½ yr.	Normal
7	3 yr. 4 mo.	Normal
8	1 ½ yr.	Normal
9	3 yr. 9 mo.	Normal
10	1 ½ yr.	Normal
11	9 mo.	Normal
12	2 yr.	Normal
13	1 yr. 7 mo.	Normal
14	1 yr. 7 mo.	Normal
15	1 yr. 5 mo.	Normal
16	1 yr. 8 mo.	Normal
17	3 yr. 8 mo.	Normal

is known of the factors responsible for demyelination in human encephalitis, it would nevertheless seem advisable to administer the medicament prior to the time when this degenerative change is apt to appear.

The precise mode of action by which corticotropin produces a favorable effect is speculative. Kabat and co-workers [3] have shown that in experimental encephalomyelitis the hormones have the capacity to inhibit granuloma formation, a condition which is essential for the production of the disease. As noted by these investigators, the suppression of granulomas by the hormones parallels their effects on granulation tissue in wound healing, vascularization of the cornea, tubercle formation, and degree of inflammation in allergic reactions. Modification of the granulomatous response in turn leads to antibody suppression, which is at present regarded as one of the basic mechanisms of hormonal action. Other postulated mechanisms include the capacity of the hormones to alter the permeability of small blood vessels, to prevent reflex vasomotor reactions, and to delay the movement of colloidal materials through the ground substance. If measles encephalitis is due to an allergic response of the central nervous system to the virus of measles, as postulated by Finley,[6] then the theory of antibody suppression would seem quite plausible. However, in the present state of our knowledge it is impossible to determine which, if any, of the mechanisms referred to applies to the use of corticotropin in human encephalitis.

While this series is too small to permit definite conclusions, nevertheless the favorable results obtained in all but one case suggest that corticotropin has a beneficent effect in measles encephaitis. At any rate, it is hoped that this report will encourage further clinical trial of corticotropin in measles and other forms of demyelinating encephalomyelitis.

Summary

Seventeen consecutive patients with measles encephalitis were treated with corticotropin. The daily dose of the hormone varied from 5 to 80 mg. and the total amount of the drug given individual patients ranged in most instances from 100 to 320 mg. In this series there were no deaths. at the time of discharge from the hospital only three patients showed residual neurologic stigmas. A follow-up study on 16 of these patients showed that 15 escaped without sequelae.

Dr. Thomas A. Anderson assisted in the study of these cases.

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Urethral Meatal Caliber in Circumcised and Uncircumcised Males

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Congenital or acquired stenosis of the external urethral meatus is recognized as an important cause of serious urinary-tract obstruction. When the literature is reviewed on this subject, one of the aspects often discussed is the possible influence of early routine circumcision on the integrity of the urethral meatus during infancy and early childhood in allowing development of ulcerative meatitis and its sequel, secondary stenosis. The ideas pertaining to this aspect of the subject will be briefly summarized as a background for this study.

Gairdner, in his study of circumcision, emphasizes the following points to support his belief that the prepuce should not be considered a vestigial structure that is devoid of function: 1. The prepuce is not fully retractable in 96% of male infants at birth but becomes so in all but 10% of cases by three years of age. Nonretractability at birth is not due to so-called "adhesions" or a true phimosis, as is so commonly thought, but rather to incomplete development of the prepuce at that time. Final development and spontaneous separation of the prepuce from the glans continues after birth with eventual formation of the preputial sac. 2. It is, therefore, fortunate that the prepuce is redundant and irretractable in most cases during early life, since it then may protect the glans and meatus during a period when these structures are constantly exposed to the wet diaper and clothing. This latter point is emphasized by the near-confinement of meatal ulcer in male infants and children to those who have been circumcised.

Meatal ulcer is not uncommon in male infants and children. The condition is characterized by a painful superficial ulceration about the urethral meatus which tends to dry and incrustate with partial or complete occlusion of the orifice. Due to friction or during micturition, the crusts break off with consequent further irritation and ulceration. As there is a tendency for spontaneous healing, a cycle of scarring and reulceration is set up which eventually can lead to stricture formation and urinary obstruction. The advanced case will show marked stenosis of the meatus with rhagades at the meatal angles.

Brennemann and Cooke, in the pediatric literature, focused attention on exposure of the meatus in circumcised males to the ammoniacal diaper as the cause of meatal ulcer, with stenosis developing secondarily. Muschat found that this condition was prevalent in those children with an abnormally high location of the meatus on the end of the glans. As a consequence to this, there is an associated wall or dam of tissue at the ventral meatus in front of the navicular fossa against which the urinary stream is forced during micturition. The resulting trauma was believed to be a predisposing factor in the formation of meatal ulcer. Meatotomy corrected the defect and ulcerative meatitis. Campbell believes that a preexisting congenital stenosis of the external meatus is the basic cause of meatal ulcer with infection and ulceration developing secondarily and setting up the cycle. He also advises an adequate meatotomy as treatment for this condition.

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Those and other discussions in the literature regarding the possible relationship of circumcision to ulcerative meatitis and meatal stenosis prompted this comparative study of meatal caliber in a group of circumcised and uncircumcised males. It had also been observed that a meatotomy was done oftener in circumcised males prior to being able to pass the resectoscope to do a resection of the prostate.

Method of Study

Calibration of the urethral meatus was carried out in 100 circumcised and 100 uncircumcised adult males, using the Otis bougie à boule. A similar number of circumcised and uncircumcised male infants and children up to 18 months of age (62 under 12 months) were calibrated. Subjects were selected at random from other than the urologic services at Hines Veteran's Hospital and Children's Memorial Hospital. Those patients having a history of prior urologic disease or instrumentation of any kind were not selected for this study in order to exclude, as far as possible, any factors that might secondarily effect meatal caliber. Calibration was carried to a point where there was snug accommodation of the bougie with care to avoid stretching or forcing of the instrument.

Results

In the adult group a much higher percentage of circumcised men showed some degree of meatal narrowing than did those that were uncircumcised. In the circumcised group approximately 60% had a meatal caliber of 20 F. or below, as compared with only 25% in the uncircumcised group. When the percentage of either group falling in any one caliber is compared, a considerable difference in the distribution can be seen. The bar graph shown in Figure 1 compares the number of circumcised and uncircumcised cases falling into each caliber. The number of uncircumcised cases in calibers 22 F. to 26 F. or more almost doubles, in each case, those in the circumcised group. In sizes below this, the situation is reversed with the circumcised group showing a marked majority in the lower calibers, this being particularly evident in the 18-F. through 16-F. categories. A comparison was also done between those subjects circumcised under one year of age and those where the procedure was done later in life and past the diaper age. Men undergoing circumcision early in life showed a higher incidence of meatal narrowing than did those circumcised later. The bar graph shown in Figure 2 compares the distribution of meatal caliber in cases circumcised early and later in life. There was no difference in the incidence of meatal stenosis between the Negro and Caucasian in this series. Meatal caliber in patients with a redundant prepuce covering the meatus was not significantly different from those having a short foreskin allowing con-

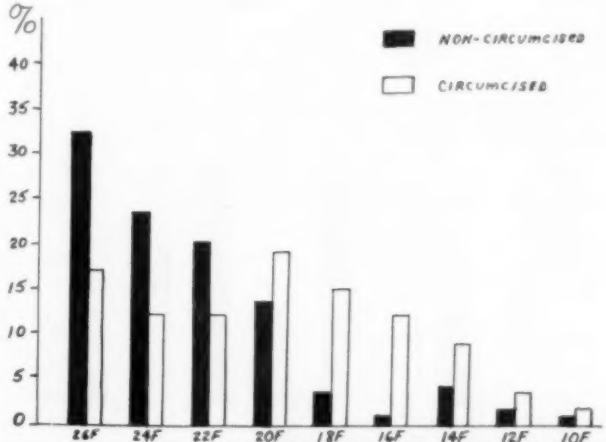

FIG 1. URETHRAL MEATAL CALIBER OF 200 MALE ADULTS IN EACH GROUP.

stant exposure of the meatus and glans penis. Interestingly, only 25% of the 200 adult cases studied showed calibers of 26 F. or more—this being the usual figure given in most textbooks as the normal caliber of the external urethral meatus in adult men.

In the pediatric group, a similar pattern was seen in the age group between 12 and 18 months (38 children), although not as striking as in the adult series. Only 30% of circumcised males in this age group had a meatal caliber of 14 F. or more, whereas 53% of the uncircumcised males fell into this category. In this age range 10% of the circumcised infants showed marked meatal stenosis with calibers below 10 F. as compared with only 3% in the uncircumcised. The infants that were calibrated at one year of age or below showed a similar distribution of meatal size in both the circumcised and uncircumcised series. Thus, it would appear that the narrowing does not take place immediately but requires time to develop.

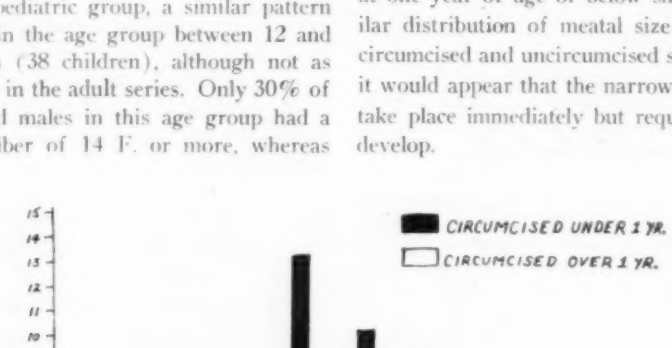

FIG 2. URETHRAL MEATAL CALIBER OF 100 MALE ADULTS CIRCUMCISED UNDER AND OVER 1 YEAR OF AGE.

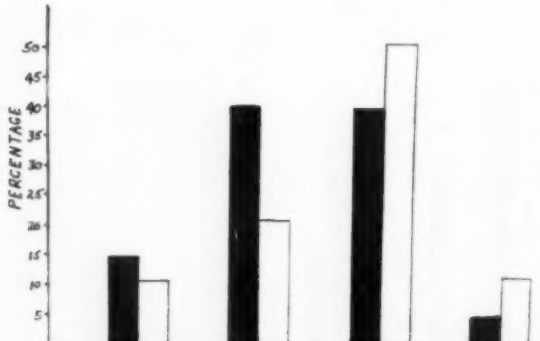

FIG 3. MEATAL CALIBER-MALES 12-18 MOS.

Comment

A definite explanation for an increased incidence, found in this study, of meatal coarctation in circumcised males cannot be given. However, with exclusion of the acquired causes of meatal stricture in the adults and children calibrated by selecting subjects free of prior urologic disease or instrumentation and assuming that congenital stenosis would manifest itself to an equal degree in both the circumcised and uncircumcised groups, the results of this study suggest a relationship between meatal narrowing and circumcision, particularly when the procedure is done early in life. It is during that period that the meatus would be most vulnerable to irritation and trauma if not protected by the prepuce. A breakdown of the delicate mucosa of the urethral meatus, whether resulting from acute ulceration or low-grade inflammation, could result in eventual secondary stenosis of varying degree in many cases.

Undoubtedly the general practitioner and pediatrician see and treat the great majority of cases of ulcerative meatitis. The urologist, in most instances, sees only the severe and complicated cases where the condition is beyond responding to "medical" treatment. Personal communication with several pediatricians and general practitioners in this area showed general agreement that the incidence of meatal ulcer is relatively high and that it occurs almost exclusively in circumcised infants and young children not yet toilet trained. In those cases where it occurred in patients uncircumcised, the prepuce was short and allowed constant exposure of the meatus. The majority of men questioned had not noted any stenosis of the ulcerative meatus preexisting in most cases, although the severer cases and those refractory to treatment did have a high incidence of meatal stenosis. Protection of the meatus and correction of the ammoniacal diaper brought about cure in most cases, although meatotomy was also frequently used.

The fact that the condition is seen occasionally in uncircumcised patients where the mechanical and chemical irritants could not play a part and the high cure rate obtained with meatotomy would also indicate the importance of preexisting meatal stenosis as a causative factor. To explain the marked difference of incidence in circumcised and noncircumcised males, it is feasible that, rather than being congenital, the stenosis in circumcised patients might develop gradually from low-grade, subclinical inflammation at the meatus as a result of mechanical and chemical irritation with typical meatal ulcer developing in some cases if the stenosis becomes more alvanced. Those cases developing in the uncircumcised, which are of much less frequency, would occur only where a congenital stricture is present.

It is not intended, in view of the findings of this study, to condemn circumcision as a procedure without merit or as a major factor causing serious meatal stenosis. Certainly, the degree of meatal narrowing found in the circumcised adult group for the most part was not of clinical significance from the standpoint of causing serious urinary obstruction. However, it does show a difference between the circumcised and the uncircumcised males who require meatotomy prior to passage of large resectoscope sheaths.

Summary

A comparative study was carried out on the caliber of the urethral meatus in circumcised and uncircumcised adult males. A definite increase in meatal narrowing was found in the circumcised group, particularly if circumcision was done at birth or during the diaper age. A similar comparison was made in infants and young children under 18 months. No difference in meatal caliber was noted in the two groups of males under one year, but an increase in meatal stenosis was again noted beyond that age in those where circumcision had been done early.

The relationship between early circumcision and the development of ulcerative

meatitis with secondary stenosis was discussed and correlated with the findings of this study.

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Hematuria Following Minimal Trauma

A Sign of Congenital Uropathy

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During the past year, major congenital anomalies of the urinary tract were discovered in three children as a result of urologic investigation of the tract because of hematuria which followed minimal trauma to the region of the kidneys. Usually attention is directed to these abnormalities of the kidney as a result of a tumor, recurrent fever, repeated episodes of urinary-tract infection, enuresis, or other findings which lead to early diagnosis and institution of therapy. On occasion, silent lesions of the kidneys, such as hydronephrosis and neoplasms, suddenly become clinically manifest after traumatic rupture with resultant hemorrhage and shock.* Although there has been an increasing awareness of the frequency of genitourinary anomalies, we feel that hematuria following minimal renal trauma has not been sufficiently stressed as a sign of congenital uropathy. Our recent experience has been so impressive that we feel that full investigation of hematuria following renal trauma in children and young adults must replace the common practice of "watchful expectancy."

Report of Cases

CASE 1.—A 12-year-old white boy was admitted to the Albany Hospital on Feb. 16, 1955, with the chief complaint of blood in the urine. While playing, he was accidentally struck in the right hypochondrium by his companion's knee. After the blow he experienced some pain which persisted and, on the third day, he noted that his urine was bloody. The pain and hematuria continued for one week and he was admitted for investigation. On physical examination, there was slight tenderness over the right flank. The urine showed 2-plus albumin and many red blood cells. The hemoglobin level was 9.5 cm. per 100 cc. and the hematocrit 33%. Intravenous pyelograms revealed hydronephrosis on the left with an apparent obstruction at the ureteropelvic junction. The right kidney and ureter were not visualized. In addition, retrograde pyelograms (Fig. 1) showed a Grade IV saccular hydronephrosis on the right side.

Fig. 1.—Retrograde pyelograms showing marked bilateral hydronephrosis due to congenital stricture at the ureteropelvic junction. Note the prominent saccular dilation of the calyces on the right.

On Feb. 22, 1955, a left pyeloplasty was performed, followed on March 7th by right nephrectomy. On pathologic examination this kidney showed moderate hydronephrosis with marked atrophy of the renal parenchyma due to congenital stricture at the ureteropelvic junction. Lacerations

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From the Departments of Urology and Pathology, Albany Hospital and Albany Medical College.

*References 1 and 2.

of the pelvis with extensive hemorrhage were also present, presumably as the result of the injury.

CASE 2.—A 6-year-old boy was admitted to the Albany Hospital on April 26, 1955, with the chief complaint of blood in the urine for 12 hours. He had been struck a glancing blow by an automobile on April 25th and had sustained minimal abrasions of the skin of the right forearm and forehead. Twelve hours after this accident, he first noted that his urine was bloody. He was hospitalized for investigation. In addition to the abrasions of the forearm and forehead, physical examination

Fig. 2.—Retrograde pyelogram showing moderate hydronephrosis with ureteropelvic obstruction on the left due to an aberrant renal artery.

disclosed superficial ecchymoses of the skin and some muscle resistance to palpation, in the right flank. The urine was grossly bloody. An intravenous pyelogram revealed slight hydronephrosis on the right. The boy was treated conservatively, and the hematuria terminated in 48 hours. On May 1, 1955, retrograde pyelograms again disclosed the slight hydronephrosis on the right, the condition apparently being due to an obstruction at the ureteropelvic junction. The patient was discharged but was scheduled to return to the urology clinic for follow-up studies in six months.

CASE 3.—A 12-year-old white boy was admitted to the Albany Hospital on Oct. 23, 1954, with the chief complaint of blood in the urine. On the day prior to admission, while playing football, he had been hit in the left flank. Shortly after this injury, he passed grossly bloody urine with clots. On the morning of admission, his urine was still bloody and contained blood clots, and there was vague pain in the left flank posteriorly. Intravenous and retrograde pyelography (Fig. 2) on Oct. 26th showed moderate hydronephrosis on the left with obstruction at the ureteropelvic junction. At operation on Oct. 28th, the obstruction at the ureteropelvic junction was found to be caused by an aberrant renal artery.

Comment

These three cases indicate that in children major congenital anomalies of the urinary tract which have been clinically silent may first manifest their presence by hematuria following minimal trauma. Each of the above patients was found to have hydronephrosis which was due to some type of congenital obstruction at the ureteropelvic junction. Hematuria was usually noted within a few hours after injury, but in one case it was not recognized until the third day. In contrast to patients who sustain severe injury to the kidneys and have bleeding, these children with underlying marked and frequently prolonged urinary congenital anomalies commonly have a relatively short but definite period of hematuria. In most of these cases the hematuria, the cardinal sign of the renal abnormality, will disappear with "expectant" therapy. However, this ideal time to identify asymptomatic congenital abnormalities while still amenable to surgical therapy must not be lost. We believe that hematuria, no matter how transient or apparently inconsequential, when it occurs in children after any type of trauma, should call for a careful examination of the urinary tract. An intravenous pyelogram should be done in an effort to identify underlying silent renal lesions. Beneficial results can be expected only when definitive surgical therapy can be instituted before the irreversible effects of the anomaly have developed.

Summary

Three case of hematuria in children following minimal renal trauma are presented. In each instance careful urologic investigation, in spite of the minor character of the

injury, demonstrated a major renal congenital abnormality.

"Expectant" therapy of transient hematuria will deny definitive diagnosis and treatment to those patients with underlying renal anomalies.

An intravenous pyelogram is the minimum study recommended in all cases of transient hematuria subsequent to minor renal trauma.

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A Simple Method for Collection and Analysis of Sweat for Chloride

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Abnormally high concentrations of sodium and chloride in the sweat of patients with fibrocystic disease of the pancreas were first noted by Darling, di Sant'Agnese, Perera, and Andersen, in 1953.[1] Papers supporting and extending this observation * appearing since that time would indicate that a high chloride concentration in the sweat is the most constant of the numerous manifestations of cystic fibrosis of the pancreas. Because of the diagnostic importance of the determination of sweat chloride, an effort has been made to devise a simpler procedure for the collection of sweat than that commonly used. In the studies mentioned above, sweat for analysis was produced by thermal stress, either by placing the subject in a room at 90 F for one to two hours † or by encasing the trunk and extremities in a plastic bag.[5] The present communication describes a method for local production of sweat by intradermal injection of a small amount of parasympathomimetic drug. In the first attempts injections of physostigmine followed by methacholine (Mecholyl) were used;[6] later it was found that a single small injection of furtrethonium (Furmethide)[7] iodide produced somewhat greater amounts of sweat and was free of the side-reactions of flushing and bradycardia noted occasionally with the physostigmine-methacholine procedure. The sweat is collected on gauze squares by the usual method in sufficient quantity to permit ready analysis of the eluate for chloride by the mercurometric titration procedure. The method appears superior to those previously described in that the sweat collection is quickly and easily performed, requires no special equipment, and subjects the patient to a minimum of discomfort.

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From the Children's Hospital and the Children's Hospital Research Foundation.

* References 2-5.

† References 1-4.

Method

Sweat Collection.—An area of abdominal skin approximately 3 in. square is prepared by first cleansing with 70% alcohol or aqueous benzalkonium (Zephiran) chloride solution and then with sterile distilled water. The skin is dried thoroughly with sterile gauze pads. In the center of the area 0.2 to 0.4 ml. of furtrethonium iodide solution, containing 0.66 to 1.3 mg. of the active agent, is injected intradermally.

Over the wheal is placed a 2×2 in. gauze pad, which, in turn, is covered by a slightly larger square of vinyl sheeting, and the dressing is sealed at the edges by adhesive tape. One hour later the gauze pad is removed and placed in a weighing dish. The weighing dish is fitted with a ground-glass cover thinly smeared with stopcock grease to make an airtight seal. The weighing dish and gauze pad are weighed and their weight before sweat collection subtracted to obtain the volume of sweat. After weighing, the cover of the weighing dish is removed and the gauze allowed to dry. To the dry gauze are added 2.0 ml. of distilled water which saturates it thoroughly. After the hands are washed, rinsed in distilled water, and dried, the water is manually wrung from the gauze and an aliquot of the eluate used for the determination of chloride.

Determination of Chloride.—In earlier attempts the microdiffusion method of Conway [8] was used for determination of chloride in the gauze eluate. Later the mercurometric titration of Schales and Schales [9] was found to be preferable in ease of procedure and economy of time.

By the mercurometric procedure a 1.0 ml. sample of the gauze eluate is pipetted into a small porcelain dish, 0.5 ml. of 1.0 N HNO_3 and one drop of diphenylcarbazone indicator are added, and the mixture is titrated with mercuric nitrate solution. The titration is most accurately done with a microburette, using a magnetic stirrer with a "flea" of iron wire encased in a glass capillary. A useful apparatus for the titration is illustrated in Figure 1. The end-point is reached when the solution turns from salmon pink to blue.

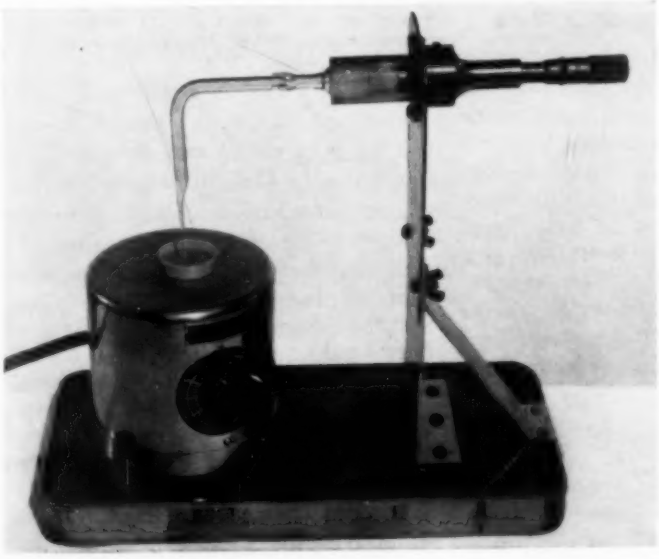

Fig. 1.—Microburette and magnetic stirrer used for chloride titration. The burette is constructed from a Warburg manometer calibrator (Micrometric Instrument Company, Cleveland) and a section of a Warburg manometer. The end of the manometer section has been drawn to a fine delivery tip. Burettes containing mercury were not satisfactory in that contact of the mercuric nitrate reagent with metallic mercury appeared to cause a change in the reagent which obscured the end-point of the titration.

Chloride concentration in the eluate is calculated as described by Schales and Schales. The volume required to titrate a gauze blank is subtracted from the volume used in the titration of the sample. In our experience the chloride concentration of 2.0 ml. eluates of plain gauze was 0.85 mEq. per liter. This difference is then multiplied by the factor obtained from the titration of standard solutions of sodium chloride to give chloride concentration in the eluate. Sweat-chloride concentration is then obtained by the expression $\frac{2.0 \text{ ml.}}{\text{volume of sweat}} \times$ chloride concentration of eluate.

Results

With the dose of furtrethonium iodide described, the amounts of sweat collected averaged about 0.3 ml., with a range of 0.1 to 1.4 ml. Rarely volumes less than 0.1 ml. were obtained; in these instances the accuracy of the method was felt to be impaired, and the test was repeated. There was no significant difference in the amounts of sweat obtained from patients with fibrocystic disease as compared with that obtained from normal subjects.

The results of sweat-chloride determination on 42 normal children, 18 with fibrocystic disease of the pancreas, and members of the families of 12 of the patients are presented in Figure 2. One family had two children with the disease. The mother of one of the patients can be seen to have had

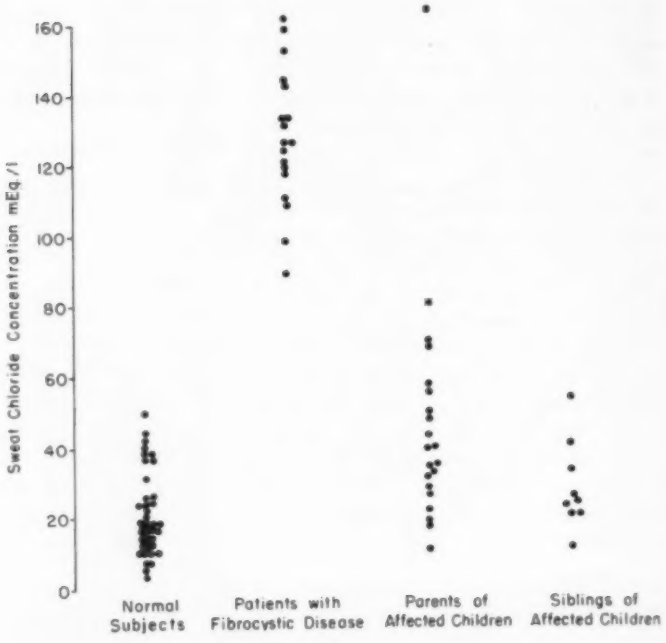

Fig. 2.—Values obtained from sweat-chloride determinations.

a sweat-chloride concentration of 163 mEq. per liter. She was asymptomatic and no further testing was done.

The ranges of chloride concentration in normal subjects and patients with fibrocystic disease are similar to those found in thermal sweat by di Sant'Agnese in a larger series of patients.[2] The single exception is that a number of his patients with fibrocystic disease had concentrations below 80 mEq. per liter, while in the present series the lowest value was 90 mEq. per liter.

Summary

A simple method of collection and analysis of sweat for chloride is presented as an aid to the diagnosis of fibrocystic disease of the pancreas.

Addendum

Since preparation of the manuscript, production of furtrethonium iodide has been discontinued. As a substitute, bethanechol (Urecholine) has been used. This drug is available in a solution containing 5 mg/ml. To perform the test, one part of the solution has been diluted with three parts 5% dextrose and 0.4 ml. (0.5 mg. bethanechol) injected intradermally. With this dose, no systemic reactions have been noted. The yield of sweat has, however, been somewhat less than with furtrethonium. In 20 tests the average volume was 0.13 ml., and 7 tests had to be repeated because the volumes were less than 0.1 ml. It is possible that a larger dose would increase the yield of sweat without producing side-effects.

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Studies of Tocopherol Deficiency in Infants and Children

II. Plasma Tocopherol and Erythrocyte Hemolysis in Hydrogen Peroxide

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Although concentrations of tocopherol in tissues or blood and estimates of dietary intake have been used as indices of vitamin E nutrition, the absence in man of recognized clinical, biochemical, or physiological correlations of vitamin E deficiency has hindered interpretation of the findings.[1] Rose and György[2] have established that hemolysis of erythrocytes in dilute solutions of hydrogen peroxide can be used as an index of tocopherol deficiency in rats and have reported that some newborn full-term infants show this evidence of deficiency.[3] In previous studies, we have reported the presence of positive hemolysis tests in premature and full-term infants fed partially skimmed cows' milk mixtures, in unfed newborn infants, both full-term and premature, and in infants and children with steatorrhea associated with cystic fibrosis of the pancreas or biliary atresia.* It is the purpose of this report to present data correlating plasma tocopherol levels and hemolysis in hydrogen peroxide of several groups of subjects: (*a*) mothers in the immediate postpartum period and normal adults, (*b*) unfed newborn infants, (*c*) thriving premature and full-term infants less than two months of age, (*d*) infants and children with steatorrhea. A similar study of a small group of premature infants has already been reported.[6]

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From the Department of Pediatrics, Sinai Hospital of Baltimore (Dr. Nitowsky), and the Department of Pediatrics of the Johns Hopkins University School of Medicine.

This investigation was supported in part by a research grant (A-494) from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, Public Health Service, and by the Association for the Aid of Crippled Children.

* References 4 and 5.

Methods

Approximately 0.5 to 1.0 ml. of blood was obtained by venipuncture from the antecubital or femoral vein with a syringe previously rinsed with sterile 1% sodium citrate in 0.9% saline solution. Samples of blood were obtained in the early morning, without regard to the time of prior feeding. The specimen was transferred to a test tube containing the residue of 2 drops (about 0.12 cc.) of a dried 1% heparin solution, and the tube was inverted several times to dissolve the anticoagulant.

An aliquot of approximately 0.2 ml. of the blood sample was transferred to a graduated centrifuge tube containing 2.0 ml. of the citrate saline solution. The hemolysis test was performed with minor modifications of the procedure of György, Cogan and Rose,[2] as described in a previous report.[5] All tests were carried out in triplicate and were begun within one hour after blood was drawn. The ratio of hemoglobin liberated from aliquots of red blood cells incubated in hydrogen peroxide and diluted with a phosphate buffer solution to that liberated by dilution in distilled water was expressed as per cent hemolysis.

The remainder of the blood sample was centrifuged for 15 minutes at 2000 rpm; the supernatant plasma was transferred to a test tube, stoppered with an aluminum-foil-covered cork, and the tube was stored at —20 C. Sufficient plasma was obtained to permit triplicate, but occasionally only duplicate, determinations of the tocopherol content. Previous studies have shown that freezing storage for several weeks at —22 C, and then thawing do not alter the tocopherol concentration of plasma. A similar stability of serum tocopherol has been demonstrated for specimens stored up to

eight weeks at −22 C.[7] The microprocedure of Quaife, Scrimshaw, and Lowry was employed to determine the tocopherol concentrations of plasma.[7] The procedure was carried out with triplicate aliquots of 0.06 cc. of plasma each, and the results were averaged. Replicate determinations were acceptable only when they agreed within ± 5%.

Blood concentrations of tocopherol have been frequently reported in samples of serum. Tests at our own laboratory as well as at others[8] indicate no difference in levels between serum or plasma samples.

Subjects

A. Mothers in Immediate Postpartum Period and Normal Adults

In 73 women on the private and service obstetrical wards of the Sinai Hospital, erythrocyte hemolysis and plasma tocopherol determinations were made during the first 24 hours of the postpartum period. Dietary histories were not obtained from any of these subjects. Simultaneous determinations were made in the newborn infants of 35 of these women. Eight female and seven male members of the hospital or laboratory staff (nurses, technicians, physicians) ranging in age from 18 to 35 years were studied. These persons all appeared to be in a good nutritional state.

B. Unfed Newborn Infants

One hundred twenty-two full-term infants born at the Sinai Hospital and fourteen premature infants born either at the Sinai or Johns Hopkins Hospital were studied before any milk feedings had been given. The birth weights for the full-term infants ranged from 2600 to 4500 gm. and for the premature infants from 1500 to 2400 gm. The results of hemolysis tests for some of these infants have been included in a previous report.[8]

C. Thriving Infants Less than Three Months of Age

1. Sixty-nine term infants were examined in the well-baby clinic of the Sinai Hospital at the time of a routine postpartum visit of the mother to the obstetric clinic. The average age was 46 days, with a range from 36 to 75 days. Fifty-five infants had been fed unskimmed cows' milk mixtures, and fourteen had been entirely or predominantly breast fed. Several had received small amounts of cereal for one to three weeks prior to the tests. Most had been given supplements of vitamins A and D and ascorbic acid since the early weeks of life.

2. Forty observations were made in 28 premature infants ranging in age from 3 to 70 days who were being fed cows' milk mixtures from which half the cream had been removed. Some of the older infants received evaporated milk mixtures for a few days prior to the final observation. Vitamins A and D and ascorbic acid were given daily as water-soluble supplements. In selected infants, the effect of feeding a water-soluble supplement of α-tocopherol acetate† on both hemolysis and plasma tocopherol level was noted.

D. Infants and Children with Steatorrhea

Observations were made in 16 infants and children with cystic fibrosis of the pancreas or biliary atresia admitted to either the Harriet Lane Home or the Sinai Hospital. The effect of supplementation with tocopherol esters was studied, using for the most part a water-soluble preparation, *d*-α-tocopherol polyethylene glycol 1000 succinate (PGS),‡ suitable for oral or intravenous administration.

Results

In Table 1 are presented the results of plasma tocopherol levels in a group of healthy adults, three groups of postpartum mothers, and three groups of unfed newborn infants. The mean value for the healthy adults, presumably on adequate diets, was 0.75 mg. per 100 cc., a level slightly lower than those reported by other

TABLE 1.—*Plasma Tocopherol Levels in Healthy Adults, Post-Partum Mothers, and Unfed Newborn Infants*

Subjects	No.	Plasma Tocopherol Mg/100 Cc.*
Healthy hospital personnel	15	0.75±0.040
Postpartum mothers†		
White private	23	1.56±0.080
White service	22	1.33±0.052
Negro service	28	1.07±0.068
Unfed Newborn infants		
Full-term		
White private	35	0.22±0.003
White service	39	0.23±0.015
Negro service	28	0.26±0.023
Premature‡	14	0.26±0.042

* Mean ± S.E.
† No dietary surveys were made for any of these subjects.
‡ Nine were white, and five were Negro.

† The preparation used was supplied by Dr. N. Berman, of the U. S. Vitamin Corporation, New York.

‡ Supplied by Dr. Stanley Ames, of the Distillation Products Industries, Rochester, N. Y.

observers.§ The three groups of mothers, all studied within the first 24 postpartum hours, showed significantly higher levels, also in accord with previous observations.[11] The average level for the group was 1.31 mg., with a range from 0.55 to 2.51 mg. per 100 cc. By arranging these subjects according to race and service, significant differences of mean tocopherol values were found between private white and service white women (difference ± S. E. difference, 0.23 mg.±0.096; $p<0.01$) and between service white and service Negro women (0.26 mg.±0.086; $p<0.01$).

The mean tocopherol levels for the unfed term infants ranged from 0.22 to 0.26 mg. per 100 cc., only from one-seventh to one-fourth of the maternal levels. There were no significant differences between the means for the newborn infants when grouped according to race and service nor between the mean for the full-term and the mean for the premature infants. The findings confirm those of other observers that newborn infants have low plasma tocopherol levels.‖ been noted in previous reports,¶ point to the relative impermeability of the placenta to tocopherol.

In Table 2 are presented the plasma tocopherol levels of thriving young infants. The full-term infants fed ordinary cows' milk mixtures showed a significant rise in plasma tocopherol, from a mean of 0.23 mg. per 100 cc. for the newborn period to 0.33 mg. per 100 cc. (difference 0.01 mg. ±0.024; $p<0.01$) by an average age of 46 days. The 14 infants who had been breast fed showed a mean tocopherol of 0.72 mg. per 100 cc., the differences from the means for unfed infants and infants fed cows' milk being significant ($p<0.01$). In the premature infants, on the other hand, feeding of partially skimmed cows' milk mixtures was accompanied by a drop in mean tocopherol levels to 0.20 mg. and 0.13 mg.

TABLE 2.—*Plasma Tocopherol in Thriving Young Infants in Relation to Diet and in Infants and Children with Steatorrhea*

	Cases, No.	Age, Days	Plasma Tocopherol, Mg/100 Cc.*
Full-term infants			
Unfed	122	Newborn	0.23±0.010
Cows' milk	55	46	0.33±0.022
Breast fed	14	46	0.72±0.071
Premature infants	26	Birth–10	0.26±0.026
(partially skimmed cows' milk)	17	11–30	0.20±0.018
	11	31 and over	0.13±0.024
Infants and children with Steatorrhea	42		0.15±0.023

* Mean ± S. E.

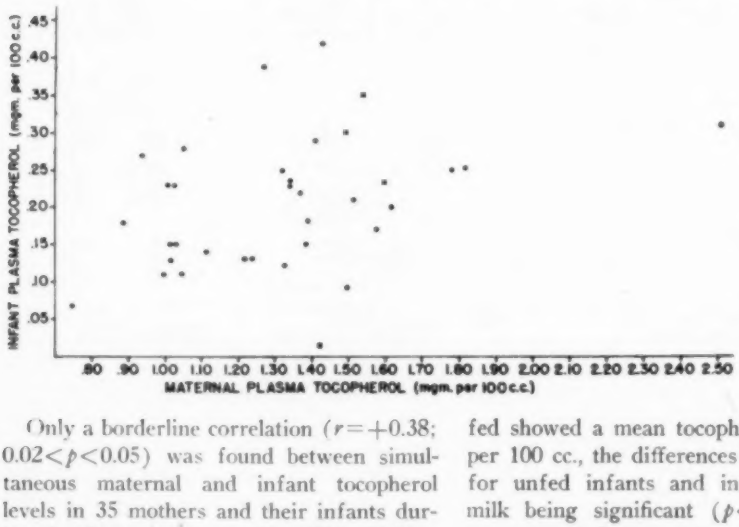

Fig. 1.—Relation between plasma tocopherol levels of mother and her newborn infant during the first postpartum day. The correlation between maternal and infant levels is only of borderline statistical significance ($r = +0.38$; $0.02<p<0.05$).

Only a borderline correlation ($r=+0.38$; $0.02<p<0.05$) was found between simultaneous maternal and infant tocopherol levels in 35 mothers and their infants during the first postpartum day. This finding, and the difference between absolute plasma levels in mothers and infants which has

§ References 9 and 10.

‖ References 8 and 12.

¶ References 13 and 14.

per 100 cc. in the infants aged 11-30 days and 31 days and over, respectively. The differences between tocopherol levels in the youngest premature and oldest premature infants (0.13 mg. ±0.035) and between the intermediate and oldest groups (0.07 mg. ±0.030) are statistically significant ($p < 0.01$ and $p < 0.05$, respectively). The trend of these results confirms that previously reported by Wright [12] and McKenzie.[6]

Forty-two observations of plasma tocopherol were made in 16 infants and children with steatorrhea prior to tocopherol supplementation. The mean level was only 0.15 mg. per 100 cc., and all but two determinations were below 0.4 mg. per 100 cc. The low levels found in these patients confirm the findings of Filer and co-workers [15] and of Darby and associates.[16]

Relation of Hemolysis of Red Cells in Hydrogen Peroxide to Plasma Tocopherol

1. *Adults.*—In the 15 healthy adults and 73 postpartum women in whom plasma tocopherol ranged from 0.55 to 2.51 mg. per 100 cc., the average hemolysis was only 4%. The highest values obtained were in three Negro women, whose erythrocytes showed 13%, 38%, and 75% hemolysis; the corresponding plasma tocopherol levels were 0.89, 1.01, and 0.55 mg. per 100 cc., respectively. This relatively uniform lack of hemolysis of erythrocytes in hydrogen peroxide when the plasma tocopherol level is above 0.5 mg. per 100 cc. is in accord with the findings of MacKenzie [6] in premature infants fed supplements of α-tocopherol acetate. In vitro addition of tocopherol shows a similar prevention of hemolysis at this level.[17]

2. *Unfed Newborn Infants.*—In Figure 2 are presented the results on 122 unfed full-term newborn infants. It is seen that for this group of infants, in whom the plasma tocopherol was below 0.45 mg. per 100 cc. in all but two instances, there was no correlation between hemolysis and plasma tocopherol. In 20 infants, even though tocopherol was low, hemolysis was 10% or less. Since it has been shown that hemolysis, when present in newborn infants, can be reversed by feeding of tocopherol,[3] one may assume that factors other than the tocopherol level alone determine whether hemolysis of red cells of these subjects will occur on incubation with hydrogen peroxide.

3. *Thriving Young Infants.*—(*a*) In Figure 3 are presented the results in 69 thriving full-term infants whose average age was 46 days. Ingestion of cows' milk or breast milk resulted in a spread of toco-

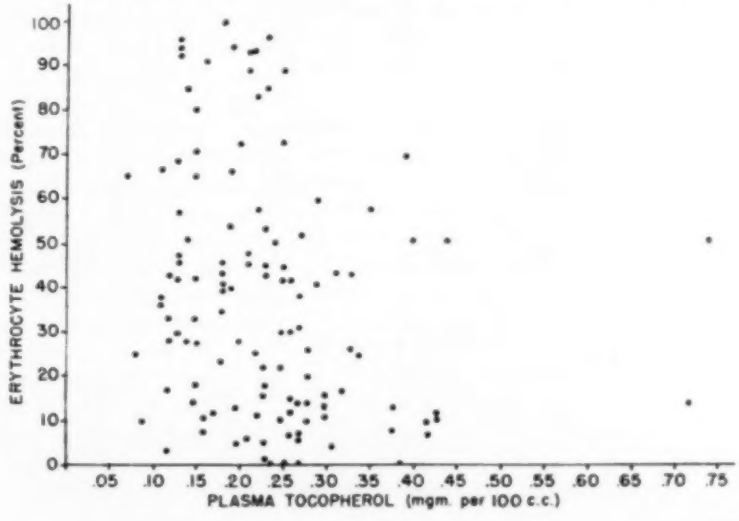

Fig. 2.—Relation between plasma tocopherol levels and erythrocyte hemolysis in hydrogen peroxide in 122 unfed full-term infants. No significant correlation was found between these values ($r = 0.03$; $p > 0.1$).

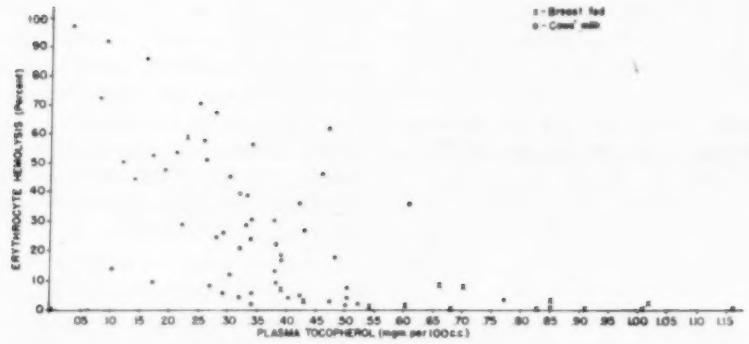

Fig. 3.—Relation between erythrocyte hemolysis in hydrogen peroxide and plasma tocopherol levels in 69 thriving young infants fed human or cows' milk. The average age of the group was 46 days, with a range from 36 to 75 days. Virtually no hemolysis was present when plasma tocopherol was above 0.5 mg. per 100 cc. Below 0.5 mg. per 100 cc. a statistically significant inverse correlation was found between plasma tocopherol and erythrocyte hemolysis ($r=-0.49$; $p<0.001$). The trend toward higher plasma tocopherol levels and lower hemolysis values among infants fed breast milk can be seen.

pherol values from less than 0.05 mg. to over 1.0 mg. per 100 cc., most of the infants fed at the breast having values above 0.5 mg. per 100 cc. It is seen that for this group of infants there is a definite trend, the higher levels of hemolysis occurring with lower tocopherol levels and vice versa. The coefficient of correlation between plasma tocopherol and red cell hemolysis at low levels of tocopherol, i.e., below 0.5 mg. per 100 cc., is -0.49 ($p<0.001$). Again in this group, there was virtually no hemolysis in infants whose plasma tocopherol was 0.5 mg. per 100 cc. and greater, only 1 of 17 observations showing more than 10% hemolysis.

(*b*) Fifteen simultaneous observations were made in premature infants more than 30 days of age. These infants had been fed partially skimmed cows' milk mixtures either entirely or almost entirely prior to testing. In some infants, tocopherol supplements had been given, but, in all, plasma tocopherol was below 0.5 mg. per 100 cc. For this group, again, a definite trend was found, greater hemolysis occurring with lower tocopherol levels and vice versa. The coefficient of correlation is -0.74 ($p<0.001$).

(*c*) In Figures 4 and 5 are presented the results in premature infants for whom serial observations were made before and after feeding tocopherol. It is seen that tocopherol levels rose promptly with the oral administration of α-tocopherol acetate and hemolysis decreased. Again, whenever the tocopherol level was above 0.5 mg. per 100 cc. there was no hemolysis.

4. *Infants and Children with Steatorrhea.*—In Figure 6 are presented the values of erythrocyte hemolysis and plasma tocopherol for a group of infants and children with steatorrhea, aged 2 months to 10 years, before and after administration of supplements of tocopherol. It is seen that virtually all the observations on untreated subjects showed plasma tocopherol levels below 0.5 mg. per 100 cc. and that in 30 of 41 observations hemolysis values were above 50%. There was a statistically significant inverse correlation ($r=-0.67$; $p<0.001$) between plasma tocopherol levels of less than 0.5 mg. per 100 cc. in treated and untreated subjects and simultaneous erythrocyte hemolysis values. When the tocopherol level was raised above 0.5 mg. per 100 cc. by administration of tocopherol esters orally or intravenously in two patients with biliary atresia, hemolysis was regularly less than 10%.

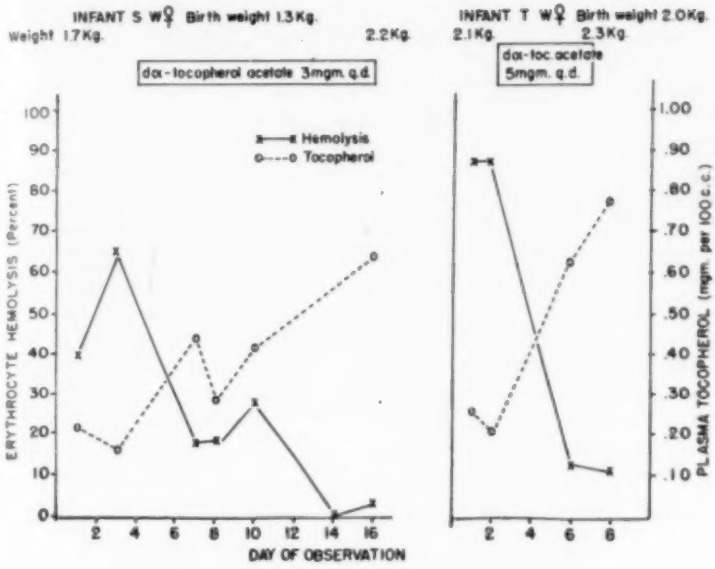

Fig 4.—Effect of small oral doses of α-tocopherol acetate on plasma tocopherol levels and erythrocyte hemolysis in two premature infants. A prompt rise of plasma tocopherol was noted with doses of tocopherol averaging 1.5 and 2.3 mg/kg/day.

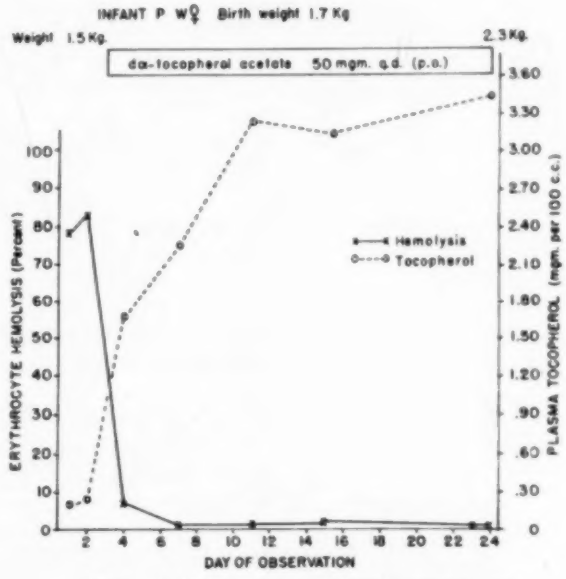

Fig. 5.—Effect of tocopherol acetate on plasma tocopherol levels and erythrocyte hemolysis in a premature infant. A prompt rise of plasma tocopherol followed the oral administration of moderately large doses of tocopherol, averaging 26 mg/kg/day.

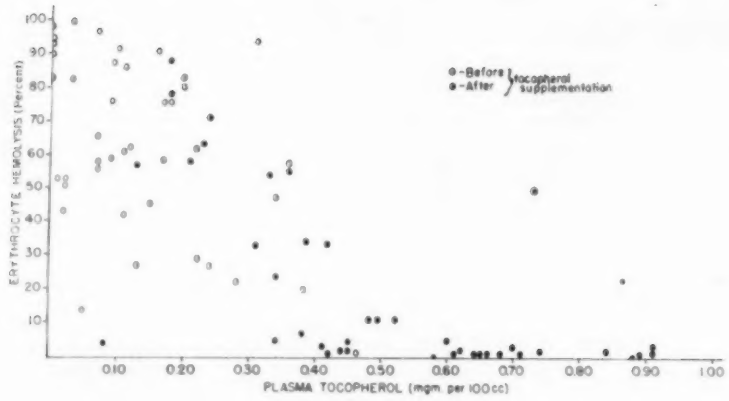

Fig. 6.—Relation between erythrocyte hemolysis in hydrogen peroxide and plasma tocopherol levels in 16 infants and children with steatorrhea due to cystic fibrosis of the pancreas or biliary atresia, prior to and following the oral administration of large doses of the acetate or polyethylene glycol 1000 succinate (PGS) esters of α-tocopherol.

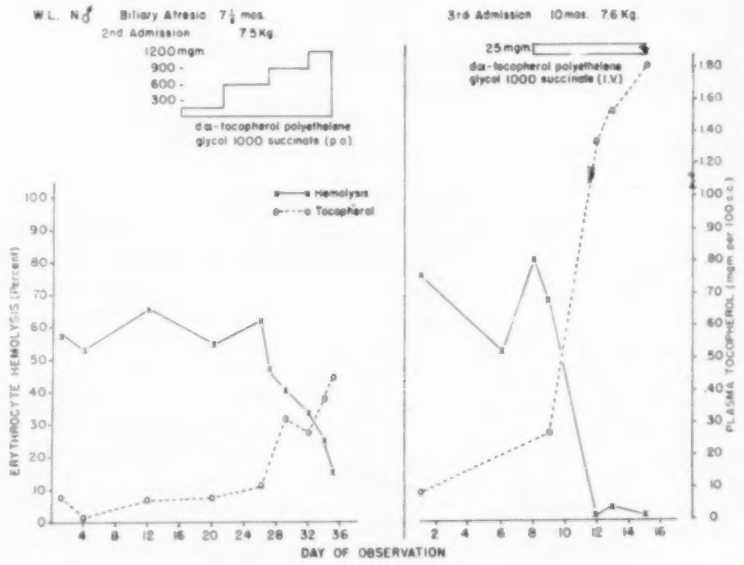

Fig. 7.—Effect of oral and intravenous α-tocopherol polyethlene glycol 1000 succinate (PGS) on plasma tocopherol and erythrocyte hemolysis in an infant with biliary atresia. The relative refractoriness to oral therapy can be seen; a prompt rise of plasma tocophernol and fall of erythrocyte hemolysis followed the daily intravenous administration of small doses of the tocopheryl ester.

In Figure 7 is presented a study comparing the effects of oral with intravenous administration of *d*-α-tocopherol PGS to an infant with biliary atresia. It is seen that oral administration of 4.0 gm. of the ester, equivalent to 1.0 gm. of free tocopherol, over a period of 10 days led to virtually no change in plasma tocopherol level or red cell hemolysis. With continued administration, the tocopherol level finally rose to 0.4 mg. per 100 cc. and hemolysis fell to 15% on the 19th day of tocopherol ingestion (total dose, 12.1 gm. of the ester). Six weeks after this massive oral dose was discontinued, the plasma tocopherol had fallen to a level of 0.09 mg. per 100 cc. and hemolysis was at pretreatment levels of 70%. With intravenous administration of the same preparation in daily doses of 25 mg. of the ester, the tocopherol level showed a

rise by the second day to 0.28 mg. per 100 cc. and by the eighth day to well over 1 mg. per 100 cc., at which time hemolysis was virtually negligible. This lack of response to oral administration except in massive doses is in striking contrast to the results obtained in thriving premature and full-term infants. In infants and children with cystic fibrosis, oral administration has led to elevation of tocopherol levels and depression of hemolysis with doses larger than those in the young infants without disease but smaller than those given to this patient and two others with biliary atresia.[18]

Comment

Studies of the susceptibility of erythrocytes to the in vitro hemolytic action of a dilute solution of hydrogen peroxide reveal an almost uniform resistance to lysis when simultaneous plasma tocopherol concentrations are above 0.5 mg. per 100 cc. At levels less than 0.5 mg. per 100 cc. a statistically significant inverse correlation usually exists between red cell hemolysis and plasma tocopherol. It is evident, therefore, that the erythrocyte hemolysis test affords a convenient screening test for patients with low plasma tocopherol levels, whether these be due to inadequate intake, digestion, or absorption. The test has been employed in this manner in patients with suspected steatorrhea and tocopherol deficiency and has also provided useful information in following the course of tocopherol therapy in these subjects.

An exception to the correlation between plasma tocopherol and erythrocyte hemolysis was found among unfed newborn infants, both term and prematures, almost all of whom showed low blood vitamin E levels. The lack of hemolysis in the presence of a low plasma tocopherol level in these subjects may be due to the fact that plasma tocopherol concentrations may not accurately reflect intracellular stores, as, for example, with ascorbic acid.[19] In addition, other properties of the red cell such as its catalase content[17] influence its susceptibility to hemolysis in the presence of hydrogen peroxide. Since many substances with the hydroquinone or quinone structure are effective in vitro in conferring resistance to hemolysis with H_2O_2,[17] it is possible that naturally occurring substances with antioxidant properties in the blood of newborn infants may affect the susceptibility of their cells to hemolysis in peroxide. While the parenteral administration of a single dose of 5 mg. of a water-soluble vitamin K derivative, menadione sodium bisulfite, to newborn infants had no protective effect upon hemolysis of their cells in H_2O_2, marked protective effect can be consistently demonstrated by incubating red cells in vitro with this substance in concentrations equivalent to those effective with tocopherol.[17] This is in contrast to the recent reports of hemolytic anemia in vitamin-E-deficient rats following the parenteral administration of large doses of a water-soluble vitamin K derivative # and of kernicterus in premature infants, presumably in association with hemolytic anemia, following the administration of vitamin K.[22] Finally, it is possible that the variation in erythrocyte size, volume, and contents, such as total and fetal hemoglobin during the early neonatal period, are related to the variable susceptibility to hemolysis in H_2O_2. The in vitro behavior in solutions of peroxide may have some relation to the life span of the red cell, which has been reported to be diminished in newborn infants.[23]

While no physiologic correlate of the in vitro susceptibility of erythrocytes to the hemolytic action of H_2O_2 has as yet been found, the phenomenon may be of importance as a model for the elucidation of the biochemical role of vitamin E in biological systems. Since tocopherols function as reversible biologic antioxidants, it has been proposed that a fundamental action of vitamin E is in maintaining the integrity of the erythrocyte by inhibition of oxidase action of hemoglobin on the unsaturated

References 20 and 21.

fatty acids of the cell membrane.*

The much higher maternal plasma tocopherol levels during the first postpartum day supports the conclusions of other investigations that the placenta is relatively impermeable to tocopherol.† This is further borne out by the borderline significance of the correlation between simultaneous maternal and infant plasma tocopherol levels in 35 cases and points out the difficulty in attempting to raise fetal vitamin E levels by administration of tocopherol to the mother.

The direct relationship between the plasma tocopherol levels in the postpartum mothers and their economic status was not unexpected in view of our previous report that an inverse relationship exists between economic status of mothers and hemolysis of red cells of the infants.[15] Some hesitancy in accepting the implications of these findings arises, however, because no dietary surveys were made for these mothers, no significant correlation between simultaneous maternal and fetal tocopherol levels was found, and, in the small group of term infants included in this report, no differences in red cell hemolysis were found among infants grouped by race and service, as noted previously in a larger sample.

The refractoriness of infants with biliary atresia to the oral administration of tocopherol in an attempt to reverse red cell hemolysis and to raise the plasma tocopherol level is of a degree which was not encountered in other children with steatorrhea. In one infant the oral administration of bile salts at the time tocopherol was being given did not influence the persistently low vitamin E level. Whether this difficulty is the result of an impairment of absorption, increased utilization, defective storage, or the slow replenishment of markedly depleted tissue stores remains for further investigation.

No clinical correlates with varying plasma tocopherol levels were noted in unfed newborn infants and in older infants on various feeding regimens. However, the recent observations of reduction of creatine excretion in children with steatorrhea due to cystic fibrosis of the pancreas [18] and in an adult with xanthomatous biliary cirrhosis [27] indicate the desirability of further studies of these subjects.

Summary

Simultaneous determinations of plasma tocopherol and lysis of red blood cells in hydrogen peroxide were made in 73 women on the first postpartum day, in 15 normal adults, in 122 term and 14 premature unfed newborn infants, in 55 term infants fed cows' milk mixtures and 14 fed breast milk, in 28 thriving premature infants fed partially skimmed cows' milk mixtures, and in 16 infants and children with cystic fibrosis of the pancreas or biliary atresia. The effect of tocopherol supplementation was determined in premature infants and in the infants and children with steatorrhea. The mean plasma tocopherols in the normal adults (0.75 mg. per 100 cc.) and in the postpartum mothers (1.07-1.56 mg. per 100 cc.) were markedly higher than those of the newborn infants (0.22-0.26 mg. per 100 cc.). Breast feeding was associated with a rise in mean tocopherol level to 0.72 mg. per 100 cc., and feeding of cows' milk mixtures, with a smaller but statistically significant rise to a mean level of 0.33 mg. per 100 cc. by average age of 46 days. Prematurely born infants fed partially skimmed cows' milk showed a decrease in plasma tocopherol from 0.26 mg. per 100 cc. in the first 10 days to 0.13 mg. per 100 cc. in infants over 30 days of age. Oral supplementation with small doses of tocopherol esters led to prompt rises in plasma tocopherol. Infants and children with cystic fibrosis of the pancreas or biliary atresia showed low plasma tocopherol levels, the average of 42 observations being only 0.15

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† References 13 and 14.

mg. per 100 cc. Oral supplementation of tocopherol esters led regularly to a rise in plasma tocopherol of patients with cystic fibrosis. In patients with biliary atresia, intravenous administration was necessary to produce consistent rises.

Analysis of simultaneous determinations of plasma tocopherol and hydrogen peroxide hemolysis indicates that when the tocopherol level was above 0.5 mg. per 100 cc. appreciable hemolysis was rarely present. When tocopherol concentration was below 0.5 mg. per 100 cc., a statistically significant inverse correlation was found in young full-term and premature infants fed cows' milk mixtures and in infants and children with steatorrhea. No correlation was found in unfed newborn infants, virtually all of whom showed low plasma tocopherol, suggesting that factors in addition to plasma tocopherol are important in determining susceptibility to hydrogen peroxide of the erythrocytes of newborn infants.

Conclusions

The hydrogen peroxide hemolysis test is a convenient method for separating patients with plasma tocopherol levels below and above 0.5 mg. per 100 cc., except in unfed newborn infants.

Evidence of tocopherol deficiency was found by one or both of these tests in virtually all unfed newborn infants, in premature infants fed partially skimmed cows' milk mixtures, and in infants and children with cystic fibrosis of the pancreas and biliary atresia. Correction of the deficiency as measured by these indices is obtained rapidly by breast feeding and less rapidly by cows' milk feeding of the full-term infants and by supplementation of the diets of the premature infants with small doses of tocopherol esters. In the patients with cystic fibrosis of the pancreas, larger oral doses were regularly effective; in the patients with biliary atresia, intravenous administration was required to obtain a consistent effect.

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Case Reports

CHORISTOMA OF THE THYMUS

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and
CAPT. D. G. JOHNSTON (MC), U.S.A.F.

DEVELOPMENT and expansion of thoracic surgery has increased the frequency with which tumors and cysts of the thymus are encountered. This has led to greater need for observation and study of anatomy, physiology, and pathology of the thymus in order to elucidate the poorly understood subject of diseases of the thymus.

An unusual lesion of the thymus will be described, and a brief discussion of the pathogenesis with suggestions for future study of thymic cysts will follow.

Report of a Case

History.—A Caucasian girl aged 2 years was admitted to this hospital on July 16, 1955, because of recurrent episodes of acute febrile illness of increasing frequency and severity since their onset at age 10 months. These were characterized by listlessness, fever, severe cough, and cyanosis, initiated by crying.

Admission physical examination revealed absence of breath sounds and dullness to percussion over the entire right hemithorax. An x-ray film (Fig. 1) revealed an opaque right hemithorax. Aspirations from the posterior right hemithorax on each of the following two days yielded 20-30 ml. of pale yellow fluid with a specific gravity of 1.009. On the fourth day, under general anesthesia, a 2-cm. incision was made in the fourth anterior interspace and a large cyst was observed to lie within the right hemithorax. This was surrounded by thick fibrous connective tissue; 250 cc. of crystal clear fluid was aspirated from the

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Fig. 1.—Opaque right hemithorax on admission posterior-anterior x-ray films of chest.

Fig. 2.—X-ray film of chest following aspiration of fluid. Aeration of the right lung is insignificant.

Fig. 3.—Aeration of right lung with elevated diaphragm on right, after removal of cyst and decortication of lung.

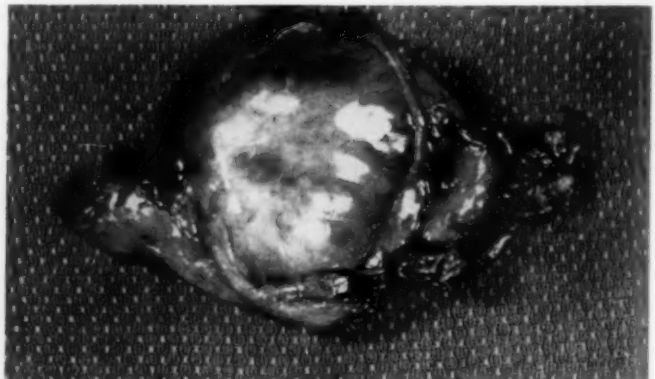

Fig. 4.—Cystic choristoma, unopened.

space. Into the cavity a large catheter connected to a water seal was placed, but, subsequently, there was very little drainage. Significant expansion of the lung was not observed to follow (Fig. 2).

An exploratory right thoracotomy was performed 11 days after admission. A cystic mass with an apparent origin from the right inferior horn of the thymus was removed. The phrenic nerve was embedded in the mass, and the diaphragm was not functioning. Decortication was performed and the right lung expanded, filling the right hemithorax. The postoperative course was uncomplicated except for x-ray evidence of an elevated, nonfunctioning diaphragm (Fig. 3).

Gross Examination.—The specimen consisted of a collapsed cyst 6×7.5 cm. in greatest dimension. One-half of the surface was smooth, glistening, and pale gray; the remaining surface was pink and rough, with fibrous tags and adipose tissue forming a pedicle. The thickness of the cyst wall varied between 0.2 and 0.5 cm. This consisted of firm, rubbery fibrous tissue and the lining was pinkish-gray and granular. A mass of soft, pink tissue, 2×2×4.5 cm., formed a part of the cyst wall near the pedicle, and two adjacent similar cysts, each 1 cm. in diameter, contained gray watery fluid. (Figs. 4 and 5).

Microscopic Examination.—The soft-tissue mass consisted of salivary glandular tissue of mucous type, with normally developed acini and intercalated ducts in a matrix of dense fibrous connective tissue. There were scattered lymphocytes, nests of parathyroid principal cells (Fig. 6) and Hassall's corpuscles (Fig. 7). An occasional intercalated duct was dilated. The cyst lining was principally of dense fibrous and collagenous connective tissue, but foci of simple columnar epithelium of intercalated duct type were present (Fig. 8). There were no abnormalities of blood vessels.

Fig. 5.—Cystic choristoma, opened. The solid portion near site of attachment was a mixture of parathyroid, thymus, and salivary glandular tissue.

Comment

This lesion, partly solid and partly cystic, was composed of a mixture of normally formed individual units of thymic, parathyroid, and salivary glandular tissue. These were abnormal only in location and arrangement and, in no area, was there an element of atypical cytological change suggestive of true neoplastic growth. While a cystic parathyroid adenoma of the mediastinum with a mixture of thymic elements has been observed,* we are not aware of a case with inclusion of salivary glandular tissue with thymic and parathyroid tissue. Malposition of adult thymus, parathyroid, and thyroid glands and/or the inclusion of part of one within another is accounted for by their embryologic development in the pharynx and subsequent caudad migration into the neck and mediastinum.[1] Such alterations, principally in migration, provide an explanation for the occasional occurrence of mediastinal parathyroid adenomas and mediastinal goiters. Displacement of tissues within another organ during the course of development is referred to as "choristoma."[3] This is not a true tumor. Teratomas, on the other hand, are probably a result of primary abnormalities in growth potentials during early embryogenesis of tissue derivatives of the pharynx and its embryologic relationships of the pharynx pouches with migratory behavior of secondary importance. Illustration of intimate and its pouches [4] provide an explanation for the particular combination of tissues of this choristoma. Normally, the tongue differentiates from the floor of pouches I and II and salivary glands arise as buds from the parent epithelium. The inferior parathyroids and thymus arise from the dorsal and

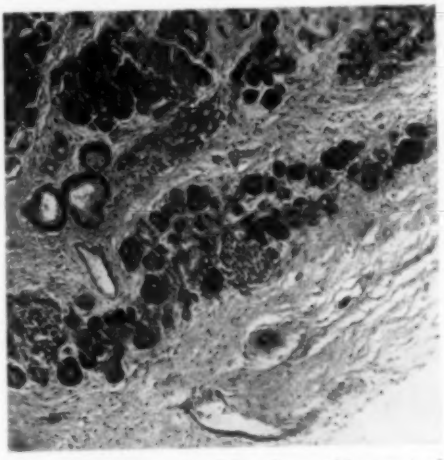

Fig. 6.—Salivary glandular tissue with a nest of parathyroid principal cells near center and intercalated ducts on right; × 60.

* References 1 and 2.

ventral wings, respectively, of the sides of pouch III.

Continued secretory activity of salivary components produced a cyst which created mechanical embarrassment of respiration as it expanded. Whether amylase was present

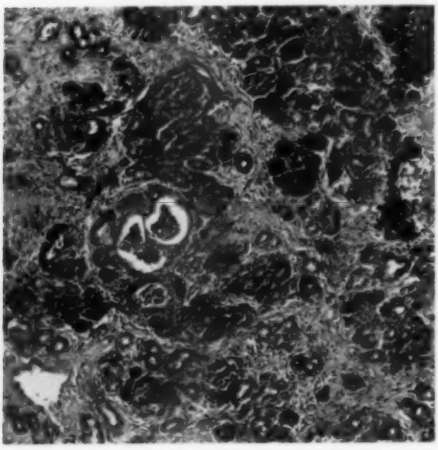

Fig. 7.—Salivary glandular tissue with Hassall's corpuscles, upper center; × 60.

within the cyst fluid and whether enzyme activity of blood and urine of this patient was increased was not determined. It would be advisable to make such tests during diagnostic and/or operative procedures on future patients with cysts of the thymus with the hope that more information concerning this entity be obtained.

While this case is not one of true neoplasm and there is no question of malignancy, it is interesting that a form of thymoma has been described to possess histological patterns reminiscent of parathyroid, thymus, and salivary glandular tissue.[5]

Summary

A cyst derived from a choristoma of the thymus is described. The lesion is benign and contains a mixture of normal histological units of thymus, parathyroid, and salivary gland.

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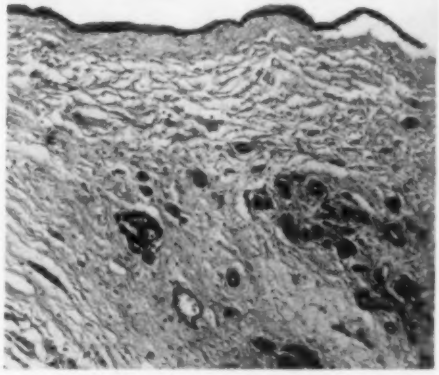

Fig. 8.—Cyst wall with salivary acini and ducts and cyst lining of ductal type, simple columnar epithelium; × 60.

TORSION OF THE SPERMATIC CORD IN THE NEWBORN

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Introduction

TORSION of the spermatic cord, or torsion of the testis in a newborn infant, is an entity rather infrequently reported in medical literature. In 1948, Campbell [1] presented two cases of torsion in the first day of life, and he considered these to be the second and third such cases to be reported; stating that the earliest record of such condition is in an article by Taylor in 1897, in the British Medical Journal. Biorn and Davis [2] in 1951 reported the fourth and fifth, and James [3] in 1953 reported the sixth and seventh cases of torsion of the spermatic cord in the first 24 hours of life. This paper will present the eighth and ninth such cases to be reported.

No doubt the entity is not as rare as the paucity of reports would indicate, for apparently many such cases are unreported. On the other hand, in the period January, 1946, to January, 1956, only one case of torsion of the spermatic cord was recorded among 10,864 births in Roper Hospital.

Many excellent articles on torsion of the spermatic cord have appeared in the literature of recent years,* and it would be needless to enter into a protracted discussion of the etiology, symptomatology, and diagnosis. These points are well known to the profession and are also readily available in current texts.[4]

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From the Department of Urology, the Medical College of South Carolina and Roper Hospital.

* References 1-3 and 5-8.

Report of Cases

CASE 1.—This white boy was a full-term spontaneous delivery Sept. 9, 1954, at 1:25 a.m. No abnormalities were noted by the obstetrician at delivery or by the pediatrician at 8 a.m. Later that day a nursing attendant noted swelling and discoloration of the right scrotum. The child was in no distress, had taken a normal feeding, and had a normal meconium stool. Examination at three p.m. by a surgeon revealed a globular cystic mass measuring 2×1½×1½ in., with purplish discoloration, without extension into the right cord, with a suggestion of incarceration, although the light source was poor and the examiner was unable to determine whether or not the mass transilluminated. His impression was hematoma of the testis, either spontaneous or due to birth injury. A possible diagnosis of torsion of the testis or testicular appendage was also entertained. The child was closely observed during the night, and there was no abdominal distension or other suggestion of intestinal obstruction. The infant was seen in consultation by me the following morning and the above findings confirmed. Final diagnosis was possible hematoma or torsion of the testis, with neoplasm to be considered. The child was asymptomatic and in no distress and discharged to be followed in the Urology Clinic. He was again seen one week later at which time the child was readmitted for exploration of the scrotum for probable torsion of the testis while also considering tumor.

On admission physical examination was not remarkable with the exception of the genital findings: The right scrotum was firm, bluish purple, acutely tender, filled with a firm mass that would not transilluminate and could not be delineated as to testis or epididymis. Discoloration extended across the median raphe to include one half of the left scrotum. That afternoon, under local anesthesia, the scrotum was explored. It was noted that all layers of the scrotum were densely adherent. On opening the tunica vaginalis, dark fluid shot forth under considerable pressure. The veins of the pampiniform plexus were dilated, twisted, and markedly discolored. The testis was tense, fluctuant, and grayish black in color; the epididymus was jet black. The cord structures were ligated as high as possible, and the testis and epididymis were removed. The scrotum was closed in layers over a Penrose drain. When the testis was sectioned, it was noted that the contents had undergone degeneration and

were mushy, with dark fluid intermingled. Postoperatively the child did well and made an uneventful recovery.

CASE 2.—This white boy was a full-term spontaneous delivery Sept. 18, 1953, at 10:19 a.m. The infant was normal except for an enlarged right testis, with indurated bluish discoloration of the right scrotum. The cord was palpable above the testis but apparently not tender and not enlarged. The scrotum over the involved area appeared slightly macerated and abraded. The boy was seen by a urological consultant † who advised exploration. At surgery at 2:30 p.m. the same date, dark serosanguinous fluid was noted in the serous cavity surrounding the right testis. There was black discoloration of the right testis and blue-black discoloration of the distal ¼ in. of the right spermatic cord. The operative record states "right testicle not properly attached to the scrotum inferiorly or posteriorly." The cord was ligated and the testis and epididymis removed. The wound was closed in layers over a Penrose drain. The left scrotum was explored and an "inadequate attachment of left testicle inferiorly to scrotum" noted. The testis was sutured at the lower pole to lateral scrotal walls with one 0000 nonabsorbable surgical (silk) suture on each side. The wound was closed in layers over a Penrose drain. The postoperative course was uneventful, and the patient was discharged on Sept. 25, 1953. Pathological section revealed extensive, diffuse interstitial hemorrhage in all structures and necrosis of varying degrees more marked in the epididymus consistent with strangulation.

Comment

Torsion of the spermatic cord is an axial rotation of the spermatic cord due to an abnormal mobility of the testis. Two varieties have been noted. In the newborn the torsion is said to occur proximal to the superior reflection of the tunica vaginalis on the cord.[4] In older children and adults the torsion occurs distal to the reflection and within the tunica vaginalis and has been attributed to either abnormal descent or anomalous serous attachments within the scrotum.‡

In older children and adults the onset of torsion is sudden and may occur at any time, even during sleep. It causes excruciating pain in the scrotum which may be referred up the cord and is often accompanied by nausea and vomiting. The testis is tender, elevated; the epididymis often can not be palpated in its usual posterior medial position.[8] The scrotal skin becomes hyperemic and edematous. An attempt to elevate the scrotum may increase the pain (Prehn's sign). In the newborn bluish discoloration of the scrotum has been reported,[2] and in these infants the above symptoms may present in varying degrees, or there may be a complete absence of subjective symptomatology.[3] The condition must be differentiated from hemorrhagic infarction of the testis, strangulated inguinal hernia, torsion of the testicular appendage, acute orchitis or epididymitis, or tumor.

If the cord structures are completely twisted so as to shut off the blood supply, the testis and epididymis will proceed to hemorrhagic gangrene unless relieved within a short time, usually cited as four to six hours. However, Klinger[9] reported a case in which the testis was perfectly normal in color and texture despite a 360 degree rotation of the cord after five days. The very short "period of grace" creates an emergency situation, and early exploration is indicated. If the testis and cord can be untwisted and color and apparent viability restored, suturing the testis to the depths of the scrotum with several sutures is indicated in order to anchor the testis to prevent recurrence of the torsion. Unfortunately orchiectomy is frequently necessary because of nonviability. The opposite side of the scrotum should be explored, and if the opposite testis is abnormally mobile, it should be anchored with several sutures to prevent torsion at a later date.§

Summary

Two cases of torsion of the spermatic cord occurring within the first 24 hours of the neonatal period have been presented. A brief outline of the etiology, symptomatology, diagnosis, and treatment has also been presented.

† Dr. P. W. Sanders Jr. Professor and Chief of Urology, Medical College of South Carolina and Roper Hospital.

‡ References 1, 4, 7, and 8.

§ References 1, 2, and 8.

Dr. P. W. Sanders Jr., Professor and Chief of Urology, Medical College of South Carolina and Roper Hospital, gave permission to include the case from his service.

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ANNULAR PANCREAS IN INFANCY

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Annular pancreas, though rare, is being reported with increasing frequency. Of somewhat more than 100 cases now reported, approximately one-third have been in infants and very young children. Kiesewetter and Koop[3] collected 25 cases in infants through 1952, including 6 of their own. Gross[2] added nine in 1953 and Rickham[6] five in 1954. These series represent the experience at large children's hospitals, and it seems reasonable to assume that isolated cases, such as that of Small and Berman,[7] have been frequent and that the true incidence is greater than is reflected in the literature.

Report of a Case

A 3½-week-old white girl was admitted to the Pediatric Service July 6, 1954, as a feeding problem. At birth, after a spontaneous full-term delivery, she showed clinical signs of mongolism, had respiratory difficulty, and was kept in an incubator until discharged 10 days later. At home she took nourishment poorly despite several changes of formula. One week before admission she vomited for the first time; subsequently she regurgitated most feedings and frequently vomited small amounts of clear fluid. No stools were passed for six days prior to admission. Family history was noncontributory.

Physical examination revealed a well-developed white female infant, moderately dehydrated, with hypotonic musculature and multiple stigmata of mongolism. There was a Grade 1 precordial systolic murmur. The bladder was distended and yielded 160 cc. of clear urine on catheterization. A soft mass palpable in the epigastrium was thought to be distended stomach. Borborygmi were present, and a saline enema produced formed stool of normal color.

A scout film showed dilatation of the stomach and proximal duodenum. There was some gas in the small bowel and the left colon. A barium enema revealed no abnormality of the colon. The infant continued to vomit lactose-water feedings and was maintained on push clyses for three days. A small quantity of thin barium mixture was then given by mouth, and it confirmed the impression of dilated stomach and duodenum. Peristaltic waves were seen crossing them; the distal portion of duodenum was visualized and was of small caliber. After one hour a considerable quantity of barium had passed into the small bowel. Oral feedings were then restarted and retained well. Stools were normal and there was a good weight gain over a two-week period. A diagnosis of partial duodenal obstruction due to stenosis, annular pancreas, or congenital band was made, and laparotomy was performed on July 23, 1954.

The abdomen was explored through a right subcostal incision. There was a failure of rotation of the midgut, with the cecum and ascending colon lying free on mesentery in the left abdomen and the duodenum and jejunum passing straight downward on the right side. There was no congenital band passing over the duodenum, and there was no volvulus of the midgut. A ring of normal-appearing pancreatic tissue 3 mm. wide surrounded the descending portion of duodenum. Proximally the stomach and duodenum were dilated; distally the bowel was of normal caliber. A side-to-side duodenojejunostomy was performed using fine interrupted intestinal nonabsorbable surgical (silk) sutures bypassing the obstruction.

Convalescence was uneventful, and the child was discharged on the 13th postoperative day taking a normal diet. On follow-up visit six months later she was eating well, gaining weight, and had no symptoms referable to the gastrointestinal tract.

Comment

Annular pancreas is unusual among congenital anomalies in that it may produce symptoms at any time from birth to late in life, or may be an incidental finding at surgery or autopsy.[8] Pathologically there is a ring of normal pancreatic tissue containing a duct and surrounding the descending portion of the duodenum. The ring is continuous with the substance of the head of the pancreas. The duodenum within the

Submitted for publication Feb. 13, 1956.

ring is constricted, and when obstruction is present it occurs at this point. The reason for the delayed appearance of duodenal obstruction in adult cases is not clear, although it may be due to attacks of pancreatitis which have been reported as occuring in conjunction with this anomaly in adults.[5] No such complications have been reported in infants.[2]

The clinical picture in infancy is one of high intestinal obstruction, partial or complete. The x-ray shows a dilated stomach and duodenum with little or no gas beyond. Associated anomalies, such as mongolism and congenital heart disease, are frequent. The clinical and x-ray findings are similar to, and cannot be distinguished preoperatively from, those of duodenal obstruction due to congenital bands, stenosis, or atresia. When this picture is present, further attempts at diagnosis by x-rays with radiopaque contrast media in the stomach, as was done in this case, do not add any necessary information and are probably inadvisable.*

The proper surgical treatment in infants is generally felt to be a bypass operation. In adults, although a proper bypass operation, i.e., duodenojejunostomy, has been successful,[1] some authors advocate a direct attack on the pancreatic ring on the basis that the anomalous pancreatic tissue is subject to recurrent pancreatitis.[5] Division or excision of the ring and plastic procedures of the Heineke-Mikulicz type on the duodenum to relieve the underlying stricture have been done but are accompanied by a high rate of complications, chiefly pancreatic fistulae.[4] Gastroenterostomy is inadequate as a bypass, since it does not drain the proximal duodenum well. In infants, however, where the primary objective is relief of high intestinal obstruction, these procedures have no place. Because the proximal duodenum is dilated, side-to-side duodenojejunostomy or duodenoduodenostomy can be done without difficulty, and the simplest effective bypass is the procedure of choice. Practically all the successfully treated cases reported in infants have been so treated, and this method is currently recommended by authors with the most extensive experience.†

Summary and Conclusions

Annular pancreas in infancy may lead to a clinical picture of duodenal obstruction similar to that produced by several other congenital anomalies. The proper treatment in infants is a bypass procedure with no direct attack on the pancreatic ring. An additional case successfully treated by this method is presented.

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* References 2 and 7.

† References 2, 3, and 6.

Correspondence

STAPHYLOCOCCUS PYOGENES PHAGE TYPE IN EPIDEMICS

To the Editor: In a recent epidemic of staphylococcal infections in the newborn nurseries at The Ohio State University Hospital, a single strain of Staphylococcus pyogenes, phage type 42B/47C/44A/52, was found to be responsible for all lesions. A report of this epidemic is to be published in *Pediatrics* (Shaffer, T. E.; Baldwin, J. N.; Rheins, M. S., and Sylvester, R. L., Jr.: Staphylococcal Infections in Newborn Infants: I. A Study of an Epidemic Among Infants and Nursing Mothers).

We have had opportunities to study organisms responsible for similar epidemics among newborns and nursing mothers in Portsmouth and Lancaster, Ohio; Lepeer, Mich.; Seattle; Hartford, Wis., and Philadelphia and have found that in every instance S. pyogenes phage type 42B/47C/44A/52 was responsible. This suggests that epidemics of this sort in newborn nurseries may be a disease entity caused by a single strain of S. pyogenes.

In all but one instance the strains from the various epidemics also demonstrated an identical pattern of antibiotic sensitivity.

Studies of this problem are being continued by the Departments of Pediatrics and Bacteriology at The Ohio State University. We would appreciate receiving cultures from pustular lesions of infants or purulent breast lesions of mothers obtained during nursery outbreaks of epidemic proportions. Reports of bacteriologic findings will be promptly transmitted.

Cultures and communications should be addressed to The Phage Typing Laboratory, Department of Bacteriology, Ohio State University, Columbus 10, Ohio.

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Abstracts from Current Literature

The Journal of Pediatrics, St. Louis

48:1-128 (Jan.) 1956

*Myocarditis in the Newborn Infant. S. N. Javett, S. Heymann, B. Mundel, W. J. Pepler, H. I. Lurie, J. Gear, V. Measroch, and Z. Kirsch.—p. 1.
Rectal Temperatures of Term Newborn Infants with Apnea. J. H. McClure and W. L. Caton.—p. 23.
Electroencephalographic Changes in Children with Artificially Induced Hyperthermia. H. W. Baird III and J. M. Garfunkel.—p. 28.
Retrolental Fibroplasia. R. Hepner, M. C. Fletcher, M. M. Desmond, H. Hunt, and S. Brandon.—p. 34.
The Incidence of Milk Allergy in Pediatric Practice. C. Collins-Williams.—p. 39.
Thrombocytopenic Purpura in Measles. J. B. Hudson, L. Weinstein, and T. Chang.—p. 48.
Unilateral Renal Hypertension in a Girl Cured by Nephrectomy. O. Kobayashi and S. Sakaguchi.—p. 57.
Temporary Adrenal Insufficiency with Associated Pyloric Stenosis. P. Rosenberg.—p. 63.
Severe Respiratory Depression Following Nasal Instillation of Tetrahydrozoline Hydrochloride. E. Chusid, D. Lehr, and W. Levy.—p. 66.
Bilateral Renal Agenesis and Oligohydramnios. G. W. Selby and A. H. Parmelee Jr.—p. 70.
Pterygium Syndrome. A. Emed.—p. 73.
Intrapericardial Teratoma. J. Basora-Defillo and F. Lichtenberg.—p. 77.
Present Status of Radioisotopes in Pediatrics. W. A. Reilly.—p. 96.
Parent Resistance to Need for Remedial and Preventive Services. M. C. Hardy.—p. 104.

Myocarditis in the Newborn Infant.—An epidemic is reported involving 10 newly born infants with an acute febrile illness characterized by extreme tachycardia and resulting in circulatory collapse and death in 6. The last five were carefully studied and showed myocarditis by clinical or histological findings in four and encephalitis in one. Excellent case descriptions are given with good photomicrographs of the histological findings of myocarditis, encephalitis, and necrosis in the splenic and lymph-gland follicles.

Evidence for Coxsackie Group B virus infection was found in four of the infants. Baby mice inoculated with brain suspensions from two fatal cases showed lesions resembling those produced by Coxsackie Group B virus. Similar lesions were produced by stool suspensions from two recovered infants, and from one of these a Coxsackie Group B Type 3 virus was identified. It must be recognized that this does not prove the etiology, but the findings are suggestive. An added note records an additional infant dying at 9 days of age with signs of myocarditis from whose myocardium a Coxsackie Type B virus was isolated.

The Journal of Tropical Pediatrics, Calcutta, India

1:189-236

Treponemal Diseases of Children in the Tropics. R. R. Wilcox.—p. 191.
*Kwashiorkor in Uganda and Coonoor. C. Gopalan.—p. 206.
Maternal and Child Health Services in S.E. Asia: (1) India. P. Robinson.—p. 220.
Accident Prevention in Childhood. F. W. Clements.—p. 227.
Rickets in the Tropics. E. Stransky and P. O. Dizon.—p. 232.

1:127-188 (Dec.) 1955

Editorial: Mongolism in Non-Caucasian Children.—p. 127.
Child Health and Parental Care. A. Burgess.—p. 129.
Observations on Amino Acid Metabolism in Kwashiorkor. M. W. Cheung, D. I. Fowler, P. M. Norton, S. E. Snyderman, and L. E. Holt Jr.—p. 141.
Kwashiorkor in Bangkok. A. Netrasiri and C. Netrasiri.—p. 148.
The Effect of Economic Background on Body Size of Chinese Infants in the First Year. J. Millis.—p. 156.
The Danger Period During Weaning: Part III. H. F. Welbourn.—p. 161.
*Ascariasis in the Tropics. E. Stransky and A. Reyes.—p. 174.

Kwashiorkor in Uganda and Coonoor.—Kwashiorkor, characterized by edema, stunted growth, a fatty liver, and skin and hair changes, is now recognized as being due to protein malnutrition in infancy and childhood. This paper compares the etiological background and clinical picture of this syndrome in South Africa and in South India. Although the dietary histories were unreliable, it appears that infants of about two years of age get little more than 20 gm. of protein a day. However, the diet offered was not the only factor, for those without Kwashiorkor had just as poor diets. Psychological anorexia may

have been a factor in initiating the acute syndrome in some of the children. In most of the children acute infection or intestinal infestations appeared to play a precipitating role in lowering the protein intake below the critical level as well as in increasing the protein requirement. The lack of a better diet is primarily due to poverty, but the faulty dietary habits of the Africans was more important than poverty itself. In India poverty was more important than in Africa.

In general the clinical picture was the same in the two countries. Treatment was with powdered skimmed milk and sometimes sweet banana. Where milk was not available, soy, cottonseed, or pulse preparations are being studied as protein substitutes.

Ascariasis in the Tropics.—This paper is essentially a review of the literature stressing the magnitude of the problem of ascariasis in the Philippines. Because of the high worm counts, complications are also commoner, such as intestinal obstruction and perforation. Of particular interest is the author's report on the treatment of these seriously ill children with papain. Papain is not toxic but acts by digesting the worms in the intestine. It was also noted that several children with heavy Trichuris infestations became free of these worms also. Since Trichuris infestations are notoriously difficult to eradicate, this is a promising finding. They gave the papain (Vermizyn) in doses of one teaspoonful one and one-half hours apart for three doses on an empty stomach.

Medizinische Klinik, Berlin

51:165-168 (Feb. 3) 1956

* Subacid Gastritis in Children. H. G. Ilker and J. Brock.—p. 165.

Subacid Gastritis in Children.—On the basis of 75 observations a disease is described as subacid gastritis, which occurs mainly in the age group of 9-11 years. Clinically it is characterized by abdominal pain usually in the epigastrium occasionally with tenderness on pressure. Sometimes attacks resembling navel colic occur. The pain may last over weeks or months interrupted by longer or shorter intervals. The children's growth in length and weight was below normal. Only about one third had nausea and vomiting. The appetite was not affected much. The acidity of the gastric juice was always below normal even when some free hydrochloric acid was present. In four-fifths of the children the total acidity was depressed. The gastric juice always contained excessive amounts of alkaline mucus (N.B., it is stated that of 17 children whose stomach juice contained some free hydrochloric acid, 7 secreted an increased amount of mucus while 10 did not). On x-ray examination gastritic changes were found in 23 cases. The majority of the cases were seen in the three years following the war when a coarse diet rich in carbohydrate but poor in constituents stimulating gastric secretion prevailed. It is acknowledged that the disease "subacid gastritis" is not sharply defined. With the therapy advocated a clinical cure was ascertained in days or after one week while restitution of acidity and mucous secretion may take longer. The multifacet therapy is discussed.

New England Journal of Medicine, Boston

254:1-44 (Jan. 5) 1956

*Persistence of Antitoxin Levels After Tetanus-Toxiod Inoculation in Adults, and Effect of a Booster Dose After Various Intervals. J. M. Looney, G. Edsall, J. Ipsen Jr., and W. H. Chasen.—p. 6.
Marked Hypoglycemia Associated with Nonpancreatic Tumors. R. S. Silvis and D. S. Simon.—p. 14.
Treatment of Leprosy: I. Chemotherapy. J. A. Doull and R. R. Wolcott.—p. 20.
Rickettsialpox: Report of a Seriologically Proved Case in Cleveland. P. D. Hoeprich, G. T. Kent, and J. H. Dingle.—p. 25.

254:45-86 (Jan. 12) 1956

*Studies in the Home Treatment of Streptococcal Disease: II. A Comparison of the Efficacy of Oral Administration of Penicillin and Intramuscular Injection of Benzathine Penicillin in the Treatment of Streptococcal Pharyngitis. D. N. Mohler, D. G. Wallin, E. G. Dreyfus, and H. J. Bakst.—p. 45.
Congenital Capillary Hemangiomas of the Parotid Gland: A Lesion Characteristic of Infancy. J. S. Campbell.—p. 56.
Salpingitis Due to Enterobius Vermicularis: Report of a Case. E. J. Croce, W. F. MacGillivray, and J. Murphy.—p. 67.

Persistence of Antitoxin Levels After Tetanus-Toxoid Inoculation in Adults, and Effect of a Booster Dose After Various Intervals.—This study is of 144 World War II veterans who had gone 4 to 10 years since their last injection of toxoid. After bleeding

they were reinjected with standard alum-precipitated tetanus toxoid and rebled at 6 and 14 days, and 68 were bled again one year later. All but one of the men adequately tested showed a good postinoculation response irrespective of the interval elapsing since the primary inoculation. One can, therefore, rely on a booster to bring up the antitoxin levels as long as 10 years later. In certain instances of major injury or if previous immunization cannot be determined, combined immunization with antitoxin and toxoid is suggested.

Studies in the Home Treatment of Streptococcal Disease.—In a previous paper this group found that more than one-third of the patients would fail to keep up a home course of oral penicillin for β streptococcal pharyngitis. For this reason a study was undertaken to compare the efficacy of intramuscular benzathine penicillin with oral penicillin. One group of 127 patients were treated with 200,000 units of buffered potassium penicillin G by mouth three times daily for seven days. After this a group of 196 patients were treated with benzathine penicillin by injection (children under 15 received 600,000 units; those over 15 years received 900,000 units).

The results showed that 94.4% of those treated with benzathine penicillin remained culturally negative 21 days after treatment compared with only 82.4% negatives in those treated with oral penicillin and tested at the end of 10 days. Part of the failures could be attributed to the patient's failure to take the full prescribed course of oral penicillin, but there was still a statistically significant difference in those who did cooperate fully. There was discomfort at the site of injection in 70% of the patients; but only 0.8% had any possible systemic reaction. It is concluded that intramuscular benzathine penicillin is cheaper, more effective, and more reliable than oral penicillin for treating Beta streptococcal pharyngitis.

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Maturation Time of Reticulocytes in Newborns, Infants and Prematures and the Lifespan of Erythrocytes in Newborns. W. K. Kunzer.—p. 249.

Rhythm of Diuresis in Children: I. Variations of Diuresis During 24 Hours with Experimentally Increased Fluid Intake. H. Rodeck and R. Kaulen.—p. 261.

P. A. H. (p-Hippuric Acid) Elimination Time as Kidney Function Test in Children and Adults with Utilization of the Capillary Blood Method. G. Essigke and G. Heuchel.—p. 271.

Chylomicrography and the Physiology of Fat Absorption in Infants. J. Jochims and G. Doerks.—p. 278.

The Diagnosis of Dysporia Entero-Broncho-Pancreatica (Fibrocystic Disease of the Pancreas). A. Stuve.—p. 293.

The Rothmund Syndrome. P. Habermann and M. Fleck.—p. 306.

*Sex Determination by Chromosomes in Cases of Absent Gonades and the Differentiation of Sex Organs. W. Ehrengut.—p. 322.

The Influence of Hormonal Factors upon the Course of Constitutional Panmyelopathy with Multiple Malformations (Fanconi Syndrome). H. G. Arlt.—p. 336.

The Virus Etiology of Interstitial Pneumonia in Infants. L. Moser.—p. 349.

77, No. 4, 1955

Phenylpyruvic Acid Idiocy (12 Observations). H. Schoenenberg, D. Schmidt, and J. Wonckhaus.—p. 363.

Recessive Sex-Linked Micro-Ophthalmia with Multiple Malformations. W. Lenz.—p. 384.

Neuroblastoma Sympathicum: Discussion and Clinical Observations. K. D. Bachman.—p. 391.

An Epidemic of Enteritis Due to E. Coli 111:B4:H12 and 111:B4:—. C. Wunderlich.—p. 413.

Hamartoma with Pellicle of the Liver (Diagnosis, Histopathology and Treatment of Liver Tumors in Children). W. Maier.—p. 422.

Spontaneous Pneumothorax as Complication of Interstitial Pneumonia. G. Schwinn and L. Heinz.—p. 433.

*Results of Sphygmographic Blood Pressure Measurements in Infants. U. Keuth.—p. 443.

Rostockian Type of Combination of Multiple Malformations (Polydactylism, Hypospadias, Cryptorchidism, and Micrognathia). O. Hovels and F. Mullereisert.—p. 454.

Acute Benign Hydrocephalus Due to Hypervitaminosis A (Syndrome of Marie-See) in Keratomalacia. W. Ehrengut.—p. 468.

Sex Determination by Chromosomes in Cases of Absent Gonads and the Differentiation of Sex Organs.—The cases of three children (15½, 14, 6) with congenitally absent gonads are reported. (The same author had reported three earlier cases: Ztschr. Kinderh. 1954).

The diagnosis was made on the basis of the increased titer of gonadotropin in the urine. Clinical symptoms consisted of retardation in growth, absence of secondary sex characteristics, and associated malformations, such as cubitus valgus, pterygium colli and stenosis

of the aorta. Ossification centers and teeth did not deviate from the norm. Differentiation from pituitary or thyroid disease was made on the basis of blood chemistry and bone x-ray findings. All six cases observed by the author were females, such malformation being unknown in the male.

Animal experiments showed that the destruction of the gonads in the fetus before differentiation of the sex organs resulted in the formation of female sex organs. Microscopic examination of the chromatin structure of the nuclei of the stratum spinosum of the skin clearly showed the presence of "sex chromatin" in females (probably the union of the 2 X chromosomes) and its absence in the male. Only two of the observed cases showed sex chromatin in the nuclei and thus were females. Since all six cases had female sex organs, the author concludes that in humans, too, the presence of testicles is necessary for the development of male sex organs, whereas in the absence of female or male gonades female sex organs develop.

The administration of follicle hormone produced menstrual bleeding also in the "male" cases and was emotionally of benefit to the patients. The genetically true sex was not explained to the patients.

The absence of the specific dynamic action of protein and disturbances of the serum phosphorus levels and the growth disturbances in these patients are briefly discussed by the author.

Results of Sphygmographic Blood Pressure Measurements In Infants.—The measuring of arterial blood pressure by the indirect method in infants suffers greatly due to the great variation in given normal values and the discrepancy with the findings by the direct method.

The author studied the results on the basis of 1200 readings on 69 healthy infants between the ages of 1 and 5 months. The width of the cuff and its application was standardized according to specifications by M. Robinow and others. (Accuracy of Clinical Determination of Blood Pressure in Children, *Am. J. Dis. Child.* 58:102, 1939). The appearance and disappearance of the pulse was recorded by means of a microphone connected with an electrocardiograph (Brecht, K., and Boucke, H.: New Electrostatic Infraton Microphone and Its Application in Sphygmography, *Arch. ges. Physiol.* 256:43, 1952). The problems of the methods of indirect blood pressure measurements were discussed by the author in an earlier publication in this journal (76:107, 1955). Readings were taken over periods of 24 hours in 2- to 3-hour intervals under various conditions (sleep, waking, food intake).

The 24-hour mean of the systolic blood pressure in the awake but quiet infant was 101.71 mm. Hg (96% of the infants fell within a range of ± 20 mm. Hg). The mean diastolic pressure was 60.16 mm. Hg, and 94% of the infants had values of ± 20 around the mean. The mean pulse pressure was 41.55 mm. Hg (83% of the infants fell within a range of ± 12 mm. Hg). These findings correspond well to those found by direct methods.

As the infant fell asleep the systolic pressure fell an average of 7.7 mm. Hg, the diastolic 6.0 mm. Hg, reaching 93.99 mm. Hg and 54.12 mm. Hg, respectively (± 20), about 15-20 minutes after sleep set in.

During the transition from sleep to eating, an increase of 26.4 systolic and 25.2 diastolic pressure was noted. During the transition from a quiet waking state to feeding, an increase of 18.7 and 19.1 mm. Hg, respectively, was recorded. These increases depended on the intensity of the sucking process and were minimal if the child was spoon fed. Ten to fifteen minutes after feeding the blood pressure returned to normal waking values.

Variations of the blood pressure during the 24-hour period (independent of sleep, etc.) as known in adults were minimal and could not be validated due to concurrent changes in the environment (ward routine). Individual, seemingly spontaneous fluctuations of 5 to 20 mm. Hg were common. An increase in systolic and diastolic blood pressure (awake and asleep) with increasing age was noted but was minimal and the number of cases too small to be statistically significant.

Diseases of Blood, Heart and Blood Vessels, and Spleen

SPLENECTOMY. S. J. EELKMAN ROODA, Nederl. tijdschr. geneesk. 98:1348 (May) 1954.

The role of the spleen in diseases of the blood is discussed. Splenectomy was done in 35 cases of congenital hemolytic anemia, with good results in 33 cases. The histological findings of Leffler in congenital hemolytic anemia could not be confirmed, marked proliferation of lymphocytes in the perifollicular margins was found in only 3 out of 12 spleens.

Of 18 patients who were splenectomized because of primary thrombocytopenic purpura, 8 died. In two patients the cause of death was a cerebral hemorrhage caused by unrelieved thrombocytopenia.

VAN CREVELD, Amsterdam.

NECROSIS OF THE HAND AS COMPLICATION OF HEMOPHILIA. W. J. H. SCHMIDT, Nederl. tijdschr. geneesk. 98:1506 (May 29) 1954.

After a blunt lesion of the lower arm a circulatory disturbance developed in a hemophiliac, causing necrosis of the hand. This may have been due to obstruction of the arteries following hemorrhages in the vascular wall.

As regards treatment of hemorrhages in hemophiliacs the continuous administration of the antihemophilic factor in the form of blood or plasma by means of intravenous droplet infusion until the hemorrhage has definitely been stopped in the author's opinion is preferable to intermittent administration of the antihemophilic factor.

VAN CREVELD, Amsterdam.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

TRANSMESENTERIC HERNIA IN INFANT. PETER W. STONE, Ann. Surg. 139:244 (Feb.) 1954.

A case of intestinal obstruction in a 17-day-old baby boy resulting from an unusually situated mesenteric defect is presented.

A brief review of the types of intra-abdominal hernia, with particular reference to mesenteric developmental abnormalities, is included.

BANTIN, Omaha.

PRIMARY GALLBLADDER DISEASE IN CHILDREN. FRANK GLENN and MALCOLM R. HILL JR., Ann. Surg. 139:320 (March) 1954.

The facts that less than 400 cases of proved primary gall bladder disease in children have been reported to date and that autopsy records of children aged 0 to 15 years show an incidence of 0.28% of cholelithiasis, as compared with 11.6% in adults over 20 years, makes the problem of gall bladder disease in children seem minimal.

It has been the authors' experience that children and young adults continue to report long-standing histories of recurrent upper abdominal pain, colic, vomiting, and transient jaundice, consistent with gall bladder disease yet unrecognized for long periods of time.

Seven cases of acute and chronic cholecystitis in children of ages 1 to 15 years are presented.

Cholecystectomy is the treatment advised for primary gall bladder disease in children.

BANTIN, Omaha.

PRIMARY NEOPLASMS OF THE LIVER IN INFANTS AND CHILDREN. GEORGE B. PACKARD and HAROLD D. PALMER, Ann. Surg. 142:314-227 (Aug.) 1955.

Nine cases of primary liver tumor in children are reviewed as to presenting signs, treatment, and pathologic findings.

No case of primary liver-cell carcinoma has survived over 22 months, although removal was considered adequate in two. All liver tumors should be considered primarily as surgical problems and demand wide resection whenever this is possible. Three benign tumors of large size threatening life were successfully treated by surgery, and one malignant tumor of blood-vessel origin apparently disappeared under roentgenotherapy. Thus, four of the nine patients are living and apparently well. These figures emphasize the fact that surgical removal of tumors of the liver in infants and young children is mandatory whenever pos-

sible and without regard to size of the tumor. When removal is not possible, biopsy is indicated in order that radiosensitive neoplasms may be detected.

Limited biopsy may not give a true sample of the whole tumor structure. It must be considered that some tumors may be removed in a premalignant stage, and it is even reasonable to suppose that some primary liver-cell carcinomas may be successfully removed, as has been reported in older patients.

BANTIN, Omaha.

OPERATIVE MANAGEMENT OF CONGENITAL INTESTINAL ATRESIA. EDWIN W. GERRISH, Ann. Surg. 142:469-477 (Sept.) 1955.

The author presents a method of management of intestinal atresia below the ligament of Treitz. He feels that the most important factor in the successful treatment is a period of adequate decompression of the distended loop proximal to the anastomosis.

In a series of 10 consecutive patients, there were three deaths. Of the seven successful cases six infants are growing and developing normally. The other infant is exhibiting intermittent symptoms of partial intestinal obstruction and may require further surgical therapy.

All 10 cases were reported in detail.

BANTIN, Omaha.

RESECTION AND PRIMARY ANASTOMOSIS OF THE JEJUNUM AND ILEUM IN THE NEWBORN. CLIFFORD D. BENSON, Ann. Surg. 142:478-485 (Sept.) 1955.

In this paper the author reports his experience with resection and primary anastomosis of the jejunum and ileum in 14 newborn patients during a six-year period.

BANTIN, Omaha.

ACUTE ULCERATIVE COLITIS DUE TO KLEBSIELLA: REPORT OF CASE FOLLOWING PENICILLIN THERAPY. EDGAR ROSEN, California Med. 80:322 (April) 1954.

A case of acute ulcerative colitis secondary to penicillin therapy is presented. The causative organism appeared to be Klebsiella Type 2 (B), which was present in pure growth on cultures of stools. Cure followed the administration of Terramycin, which was the most effective agent in vitro.

The subject of enterocolitis due to antibiotics is briefly discussed.

PRYOR, Redwood City, Calif.

PROTECTIVE EFFECTS OF LIVER IN IMMATURE RATS FED TOXIC DOSES OF THIOURACIL. BENJAMIN H. ERSHOFF, Nutrition 52:437 (March 10) 1954.

Ershoff presented findings which indicate that there is present in some batches of commercial desiccated whole liver a factor (or factors) which will counteract the growth retardation and thyroid enlargement of immature rats fed toxic doses of thiouracil. The protective factor is apparently distinct from any of the known B-vitamins. The protective effects of liver are correlated with its iodine content. Present findings indicate that some batches of desiccated whole liver and water-insoluble liver residue contain considerable amounts of thyroid hormone or some other thyroactive material and that the latter is responsible for the protective effects of these liver batches on immature rats fed toxic doses of thiouracil.

FREDEEN, Kansas City, Mo.

CHYLOUS ASCITES. C. R. LAING and R. B. SCOTT, J. Pediat. 44:191 (Feb.) 1954.

The authors report a case of chylous ascites in a Negro infant whose abdominal enlargement was first observed at the age of 2 months. Treatment included periodic abdominal paracentesis, low-fat formula, parenteral fluids, and oral vitamins. The ascites completely disappeared by the end of the first year of life. At the age of 14 years the child is apparently normal. The cause of the ascites in this patient was not determined.

MACDONALD, Pittsburgh.

FAMILIAL INCIDENCE OF CLEFT PALATE. RALPH SCHWARTZ, J. Speech & Hearing Disorders 19:228 (June) 1954.

A review of the literature and a study of 235 histories of cleft palate show that the sex ratio in cleft palate births is probably in the neighborhood of 1.5 in boys to 1. in girls. Cleft palate occurs more frequently in the families of cleft-palate cases than in the families

of non-cleft-palate cases. Heredity probably plays an important role in the etiology of cleft palate. Environmental factors, however, are also important.

PALMER, Wichita, Kan.

CONGENITAL EVENTRATION OF THE DIAPHRAGM. OLIVER E. LAXDAL, HECTOR MCDOUGALL and GILBERT W. MELLIN, New England J. Med. 250:401 (March 11) 1954.

The authors review the subject of congenital eventration of the diaphragm. This condition is described as a ballooning of one leaf of the diaphragm high into the chest. Normal costal attachments are maintained.

The cause may be congenital insufficiency of the diaphragmatic musculature, phrenic nerve paralysis, trauma, pulsion force from masses below, or traction force from intrathoracic pulmonary contractures. The lesion is usually unilateral and occurs (in adults) in one out of 10,000 persons, predominantly men.

The pathology is described. The symptoms of this disorder may be absent in half the cases. When they occur they are due to the impairment of function of the cardiovascular, respiratory, or gastrointestinal systems. Consequently, cyanosis, dyspnea, and tachycardia may occur in infants, whereas adults complain of fullness after meals, belching, coughing and wheezing, shortness of breath, hiccups, etc. This condition can rarely be elucidated by physical examination alone, and roentgenologic methods provide the only decisive means of diagnosis.

Other conditions to consider are listed, and details of the surgical treatment are given. It is emphasized that appropriate surgical intervention at the proper time may save lives in the affected children of the neonatal group.

WHEELOCK, Denver

APPENDICITIS IN CHILDREN. STEPHEN W. MEAGHER, JOHN H. CRANDON, and ALEXANDER J. A. CAMPBELL, New England J. Med. 250:895 (May 27) 1954.

In a survey of all children under 13 years of age subjected to appendectomy at the Boston City Hospital from 1950 to 1953, 74.07% had some form of appendiceal disease. The negative diagnostic error rate was thus 25.9% and the positive rate 4%. The over-all mortality rate was 0.24%, the one fatal case occurring in a child given a spinal anesthetic.

The symptoms and signs of appendicitis are reviewed.

Among 43 patients undergoing "interval appendectomy," 20 of the 24 children subsequently located were reported improved by their parents.

Although attempts must be made to lower the rate of negative diagnostic error of this disease, caution should be exercised lest the rate of positive diagnostic error, and thereby the mortality rate, be increased.

FROM THE AUTHOR'S SUMMARY.

ANNULAR PANCREAS PRODUCING DUODENAL OBSTRUCTION IN INFANCY. WILFRED T. SMALL and CARROLL Z. BERMAN, New England J. Med. 251:191 (July 29) 1954.

Annular pancreas is a rare congenital anomaly in which the second portion of the duodenum is encircled by a band of pancreatic tissue, leading to symptoms of high intestinal obstruction. The obstruction may be minor or complete, and may be associated with common duct compression, jaundice, and secondary changes in the liver.

The authors present a case of intestinal obstruction in infancy caused by an annular pancreas and outline the anatomical, embryological, and radiographic aspects of the lesion.

The treatment is surgical, and duodenojejunostomy is the procedure of choice.

WHEELOCK, Denver

VIRAL HEPATITIS IN EARLY INFANCY: REPORT OF THREE FATAL CASES IN SIBLINGS SIMULATING BILIARY ATRESIA. ROLAND B. SCOTT, WARREN WILKINS, and ALTHEA KESSLER, Pediatrics 13:447 (May) 1954.

Three fatal cases of hepatitis with jaundice are reported in siblings, with onset at ages of 4 weeks, 1 week, and 4 months and death at 3 months, 4 months, and 9 months, respectively.

Microscopic findings in postmortem sections of the liver were consistent with a diagnosis of viral hepatitis. From known data available, the hepatitis was probably of the homologous serum type.

The mother and two living siblings exhibited laboratory evidence of liver damage.

Congenital viral hepatitis may simulate the clinical picture of biliary atresia.

Failure to include a consideration of viral hepatitis in the differential diagnosis of icterus in the very young infant may have very serious consequences, since these cases do not withstand surgical procedures, such as exploratory laparotomy, very well.

FROM THE AUTHOR'S SUMMARY.

HEMANGIOMA OF THE LIVER WITH HEART FAILURE: A CASE REPORT. ROBERT W. WINTERS, SAUL J. ROBINSON, and GEORGE BATES, Pediatrics 14:117 (Aug.) 1954.

A case is reported of multiple hemangiomata of the liver in an infant who presented signs and symptoms strongly suggesting congenital heart disease. The postmortem examination revealed no gross anomalies of the heart or great vessels but did show a heart with cardiac hypertrophy. A mechanism to explain the cardiac failure in this case is discussed.

FROM THE AUTHOR'S SUMMARY.

CLINICAL AND LABORATORY DIFFERENTIATION BETWEEN HERPANGINA AND INFECTIOUS (HERPETIC) GINGIVOSTOMATITIS. ROBERT H. PARROTT, STANLEY I. WOLF, JESSE NUDELMAN, EULAINE NAIDEN, ROBERT J. HUEBNER, E. CLARENCE RICE, and NORMAN B. MCCULLOUGH, Pediatrics 14:122 (Aug.) 1954.

Thirteen cases of herpangina and twelve cases of gingivostomatitis were studied as to etiology and clinical picture. In almost all cases the clinical impression was confirmed by virus isolation. Tests done to establish other possible etiologic agents for these diseases were either negative or not statistically significant. The importance of these findings as they apply to diagnosis and treatment is discussed.

FROM THE AUTHOR'S SUMMARY.

INTUSSUSCEPTION IN INFANTS AND CHILDREN, WITH EMPHASIS ON RECOGNITION OF CASES WITH COMPLICATIONS. JI-TOONG LING, Radiology 62:505 (April) 1954.

The author in reviewing 42 children treated for intussusception divided the cases into two groups, those without complications and those with complications. The latter included gangrene, peritonitis, underlying tumor, or other lesions as a leading point. In absence of complications there were no characteristic x-ray signs and no clinical sign of obstruction. These cases, he believes, can best be treated by radiologically controlled hydrostatic pressure reduction (barium enema). This procedure, however, is contraindicated in the presence of complications.

In this study, special attention was paid to the duration of the intussusception, physical findings, fever, leucocytosis, and x-ray examinations. None of these indications could be relied upon in determining the presence or absence of most complications. Uncomplicated cases may show markedly dilated small bowel patterns or only absence of gas and a tumor-like mass on the right side. Instances in which filling defects were demonstrated by barium enema and incarcerated ileus was found at operation are described.

Of 35 cases considered uncomplicated on x-ray examination, 7 were proved to be complicated at operation.

The author attaches importance to the preliminary film and believes that radiologically controlled hydrostatic pressure reduction should be the treatment of choice in uncomplicated cases. Simple idiopathic intussusception was thought to be a nonobstructive process and therefore generally unassociated with roentgen signs of bowel obstruction.

ANSPACH, Riverside, Ill.

CONGENITAL OBSTRUCTION OF THE DUODENUM AND MALROTATION OF THE COLON. S. DOLIN, H. H. MATHEWS, and P. E. RUSSO, Radiology 63:85 (July) 1954.

Three cases of faulty mesenteric attachment and malrotation of the colon resulting in a volvulus of the midgut and an extrinsic obstruction of the duodenum near its distal portion are reported. Two of the patients were observed to have symptoms of obstruction immediately following birth. The third patient was a boy 13 years of age who had been free from symptoms excepting at birth and of recent date. At operation all of the patients were found to have the cecum and right colon in the left upper quadrant, a large adhesive band compressing the duodenojejunal junction, and a volvulus. The freeing of the band immediately caused several loops of the small intestine to assume a normal appearance. The course from this point was uneventful. Plain roetgenograms of the abdomen and opaque media (Lipiodol) played an important part in making the preoperative diagnosis.

ANSPACH, Riverside, Ill.

THE DIAGNOSIS OF ABDOMINAL CYSTS IN INFANTS AND CHILDREN. JOHN W. WILSON, Radiology 64:178-190, 1955.

The origin, nature, and physical, pathological, and x-ray characteristics of omphalomesenteric duct, mesenteric, omental, pancreatic, choledochus, urachal and ovarian cysts, as well as miscellaneous cyst-like masses are discussed. Seven cases are illustrated by reproduced abdominal roentgenograms. The author believes that a full knowledge of the origin of these masses will aid greatly in the preoperative diagnosis and guide the surgeon at the time of the operation.

ANSPACH, Riverside, Ill.

BILE PERITONITIS IN INFANCY. PAMELA A. DAVIES and A. ELLIOT-SMITH, Arch. Dis. Childhood 30:174 (April) 1955.

Two cases of so-called bile peritonitis in infancy unassociated with trauma are reported and the available literature described.

The diagnosis, etiology, and treatment are discussed.

It is stressed that the condition is an indication for surgical treatment.

KELLY, Milwaukee.

OBSTRUCTIVE JAUNDICE IN HAEMOLYTIC DISEASE OF THE NEWBORN TREATED WITH MAGNESIUM SULPHATE. N. V. O'DONOHOE, Arch. Dis. Childhood 30:234 (June) 1955.

Theories relating to the pathogenesis of obstructive jaundice following hemolytic disease of the newborn are discussed.

The clinical features of two infants with this condition and their treatment with intraduodenal magnesium sulfate are described.

KELLY, Milwaukee.

CONGENITAL MICROCOLON. JULES LAVOIE, Canad. M. A. J. 70:197 (Feb.) 1954.

A case is reported of congenital microcolon with atresia of three portions of the small bowel. The cause is thought to be a defect of the myenteric plexus.

MCGUIGAN, Exanston, Ill.

CASES OF ACUTE YELLOW ATROPHY OF THE LIVER FOLLOWING A HEPATITIS EPIDEMIC IN INFANTS. J. LAMBRINAKOS and P. PAPATHEODOROU, Helvet. paediat. acta 9:64 (April) 1954.

Of 50 cases of epidemic hepatitis that occurred in a nursing home for babies, 10 died of acute yellow atrophy.

FROM THE AUTHORS' SUMMARY.

RETICULAR NEUROMA IN A GIRL OF THIRTEEN YEARS. A. ROSENKRANZ and F. HELMER, Helvet. paediat. acta 9:191 (June) 1954.

A case has been reported of a 13-year-old girl who became ill four weeks before hospital admission. The leading symptoms were a recurring melena and a light rigidity (defense) in the right upper abdominal quadrant. The x-ray suggested the possibility of a lymphosarcoma of the stomach. The histological finding disclosed a neurogenic tumor of a reticular neuroma type. The histological criteria, the clinical appearance, and the question of malignancy were, in brief, discussed. The therapy of choice is always the radical excision of the tumor.

FROM THE AUTHORS' SUMMARY.

NEWER ASPECTS OF THE HEPATOLENTICULAR SYNDROME. H. HORNBOSTEL, Schweiz. med. Wchnschr. 84:7 (Jan. 2) 1954.

In two cases of Wilson's disease, one in a 33-year-old woman and the other in a 14-year-old boy, BAL was administered, leading to a pronounced elimination of copper in the urine. In the first case a sunflower cataract disappeared. The duodenal cataract was also examined in this case. It did not yield higher values of copper on medication. The copper determination in the urine and the changes of handwriting are emphasized for the evaluation of the treatment. The amino-aciduria was not influenced.

AMBERG, Rochester, Minn.

PANCREAS IN ALIMENTARY INTOXICATION. NINO FRONGIA and GIOVANNI SCHLICH, Ann. ital pediat. 7:24 (Feb.) 1954.

The authors, after having studied histologically 51 pancreases of toxic infants, are of the opinion that in the initial stages of alimentary intoxication the insulin increases; in further stages, on the contrary, the secretion of hormone becomes less.

FROM THE AUTHORS' SUMMARY.

LYSATED BACTERIAL CULTURES IN TREATMENT OF ENTERIC SYNDROMES IN CHILDHOOD. S. MORI and S. BORGHERESI, Rivo clin. pediat. 53:185 (Feb.) 1954.

The authors report the satisfactory findings obtained in 17 cases of enterocolitis treated with bacterial filtrates and lysates.

FROM THE AUTHORS' SUMMARY.

PROLONGED ICTERUS IN THE INFANT. RUTH CONTRERAS, EUGENIO AMENABAR, and SANTIAGO PRADO, Rev. chil. pediat. 25:10 (Jan.) 1954.

Six infants with long-standing jaundice are analyzed and discussed. In five patients the picture appeared during the first days of life and in the other when he was about one month old. A complete review of this syndrome is presented.

FROM THE AUTHORS' SUMMARY.

PROGRESS OF THE HYPERTROPHIC PYLOROSTENOSIS TODAY. HANSKARL VON HASSELBACH and HELMUTH MUELLER, Deutsche med. Wchnschr. 79:550 (April 2) 1954.

The problem is no longer whether hypertrophic pylorostenosis of infants is always to be treated by operation or by conservative medical management. Today the question is which of these treatments is to be adopted in a given case. With the close cooperation of the surgeon and the pediatrician, the majority of patients can be treated surgically. These questions are discussed on the basis of 150 cases. With proper medical management or proper preoperative and postoperative care, as the case may be, damage to life from this disorder is practically obviated.

AMBERG, Rochester, Minn.

ULCERS IN CHILDREN OF SCHOOL AGE. M. A. LASSRICH, W. LENZ, and K. H. SCHAFER, Deutschr med. Wchnschr. 80:1337-1340 (Sept. 16) 1955.

On the basis of observations of 31 certain cases of stomach or duodenal ulcers and of 20 more probable cases, the frequency, distribution between the sexes, and various etiological factors, are discussed. The data obtained in the 31 certain cases are summarized in a table. The age of the patients at the start of symptoms varied from about 2 to 15 years, while the age at the time of diagnosis was 6 to 16 years. In 24 cases the diagnosis was made after the patient reached an age of 10 years. It is emphasized that at an early stage the symptoms may not be characteristic.

AMBERG, Rochester, Minn.

ATONIC-HYPERTONIC DYSPHAGIA OF CHILDREN. KURT NITSCH, Monatsschr. Kinderh. 102: 1-4 (Jan.) 1954.

About 25% of all "habitual vomiters" show markedly impaired esophageal function, which can be named atonic-hypertonic dysphagia. This is not strictly limited to the esophagus but can also be traced to the stomach and, less commonly, to the small intestine. It is a dysfunction of motility, is variable depending on clinical manifestations, and is alleviated by thickened feedings, feeding in the upright position, and medication with sympathetic or parasympathetic inhibitors. Two groups of infants with atonic-hypertonic dysphagia can be delineated as follows: (a) young children with habitual vomiting in whom the above picture of esophageal dysfunction usually disappears by 1½ years of age; (b) older children who vomit more persistently, with infections at which blood may appear in the vomitus. The blood seems to be due to esophagitis caused by reflux of hyperacid gastric contents into the esophagus.

HARTENSTEIN, Syracuse, N. Y.

CHOLELITHIASIS WITH PANCREATIC INVOLVEMENT IN EARLY CHILDHOOD. HEINZ KREBS, Monatsschr. Kinderh. 102:327-330 (July) 1954.

A 2 month-old infant with pertussis developed abdominal distention, transient icterus without acholic stools, and a morbilliform skin eruption. Nine weeks after the onset of

this illness the infant suddenly became dyspneic and cyanotic and died. Autopsy revealed stones in the cystic duct, perforation of the gall bladder, bile peritonitis, and pancreatic necrosis. It was postulated that pancreatic involvement may occur in the course of infectious or toxic disease processes and that both the biliary system and the pancreas may be affected. It should be mentioned that the infant suffered from "dyspepsia" prior to the onset of pertussis.

HARTENSTEIN, Milwaukee.

Nervous Diseases

POLYMYXIN B THERAPY OF MENINGITIS FOLLOWING PROCEDURES ON CENTRAL NERVOUS SYSTEM: BENEFICIAL THERAPEUTIC EFFECT OF POLYMYXIN B IN MENINGITIS DUE TO ORGANISMS OF THE COLON GROUP. J. PARK BIEHL and MORTON HAMBURGER, A. M. A. Arch. Int. Med. 93:367 (March) 1954.

Five cases of meningitis due to Pseudomonas aeruginosa are reported. Each followed a procedure on the central nervous system. The first three cases were treated with various combinations of streptomycin, penicillin, and oxytetracycline. All three of these cases had a fatal outcome. The remaining two cases were successfully treated with intrathecal administration of polymyxin B. An additional case due to a Proteus species was successfully treated with a combination of chloramphenicol and intrathecal polymyxin B.

JONES, Chicago.

MENINGITIS TREATED WITH DIETHYLAMINOETHYL ESTER HYDRIODIDE OF PENICILLIN G (NEO-PENIL): REPORT OF TWO CASES. CRAIG N. SMITH and JOHN STAIGE DAVIS JR., A.M.A. Arch. Int. Med. 93:629 (April) 1954.

The authors report two cases of bacterial meningitis successfully treated with Gantrisin and Neo-Penil. They found exceptionally high spinal fluid levels of Neo-Penil and suggest that this may be a useful therapeutic adjunct to the treatment of bacterial meningitis because of the diffusion across the thecal barrier.

JONES, Chicago.

CEREBRAL PALSY: AN APPROACH TO THE PROBLEM. PETER COHEN, California Med. 80:6 (Jan.) 1954.

A program for the cerebral palsied child has been developed in California, which has been made possible through the cooperation of the state and local departments of education, the state and local departments of health, the Childrens Hospital and Orthopaedic Hospital of Los Angeles, and the University of California School of Medicine in San Francisco. An attempt is being made to deal with not only the medical and educational needs of the cerebral palsied child but also his social and emotional problems.

PRYOR, Redwood City, Calif.

PRESENT STATUS OF SURGICAL TREATMENT OF HYDROCEPHALUS. ROBERT A. SEARS, Southern M. J. 47:50 (Jan.) 1954.

This is a brief review article of value to anyone not familiar with the present-day treatment of hydrocephalus. The advantages and disadvantages of choroid plexus coagulation, resection of herniated cerebellar tonsils, third ventriculostomy, Torkildsen operation, peritoneal shunt, and ureteral shunt are given. All cases of hydrocephalus should be carefully investigated before treatment is advised or a hopeless prognosis given. The earlier study and treatment are carried out, the better is the chance of success. No personal experiences are given, nor are any statistics cited.

LOGAN, Rochester, Minn.

THE EARLY MANIFESTATIONS AND COURSE OF DIPLEGIA IN CHILDHOOD. T. T. S. INGRAM, Arch. Dis. Childhood 30:244 (June) 1955.

During a recent survey of children suffering from cerebral palsy it was found that the average delay in a diagnosis of diplegia being made following the first visit to a doctor was over one year. This delay appeared to be due to ignorance of the early manifestations to be expected in diplegia before the late stage of rigidity or spasticity with contractures.

The early manifestations of diplegia are described as they were encountered during the survey. It is suggested that the majority of patients pass through a stage during which

they show hypotonia and a stage during which they show sudden generalized dystonic attacks on changes of position before rigidity or spasticity is evident. The stage of dystonia seems to be of shorter duration and the dystonic attacks less marked in patients with paraplegic involvement than in those with triplegia or tetraplegia. It is suggested that the diagnosis would be reached earlier in patients with diplegia if a neurological examination, including attempts to produce dystonia, was made in every suspected case.

KELLY, Milwaukee.

THE USE OF SOME ANTIBIOTICS OF WIDE RANGE OF ACTION IN SOME OF THE VIRUS DISEASES OF THE NERVOUS SYSTEM. F. TESCOLA, Clin. pediat. 36:287 (April) 1954.

The therapeutic results of the use of Terramycin, Aureomycin, and chloramphenicol on the clinical course of certain virus diseases of the nervous system were analyzed.

In poliomyelitis, even in the preparalytic phase, none of these drugs seemed to affect the course of the disease.

In other virus diseases, encephalitis, myolitis, and meningitis, chloramphenicol, given parenterally, seemed to give a quicker therapeutic response than did the other two drugs.

HIGGINS, Boston.

DIAPHRAGMATIC PARALYSIS IN INFANTS. C. ZUNIN and S. SCARABICCHI, Lattante 25: 24 (Jan.) 1954.

The cases of five young babies with paralysis of the diaphragm are reported; three were on the right side and two on the left side. In two of the cases there had been a difficult labor, in the course of which injury had occurred to the phrenic nerve. The birth was normal in the other three cases, and thus other explanations of the cause were necessary. The probable explanations in these cases were (1) hypoplasia of the muscles of the diaphragm, (2) hematoma, (perhaps from vitamin K deficiency), in the neck near the phrenic nerve, and (3) a congenital abnormality in the course of the phrenic nerve. The prognosis is usually good in cases of paralysis of the diaphragm in infants; recovery of function is usually slow, but progressive.

HIGGINS, Boston.

THE SUBSEQUENT STATUS OF PERSONS WHO HAD HAD CONVULSIONS IN CHILDHOOD. P. BRUSA, G. BIZZI, and F. BRESCHI, Minerva pediat. 7:25 (Jan. 13) 1955.

In order to make a better prognosis in the cases of children who have convulsions, 66 former patients with that condition were evaluated 1 to 18 years later by means of an interval history, physical and neurological examinations, mental tests, and electroencephalograms.

Of the 26 cases with convulsions ascribed to high fever, 8 had become epileptic, 5 showed a slow physical development, and several others EEG alterations.

Of the 21 cases where there had been endocranial hemorrhage, 17 had either definite epilepsy or a mental retardation; only 4 were normal clinically.

Of the remaining 19 cases, 9 had epilepsy and 7 were mentally retarded or disturbed; only one had a perfectly normal EEG.

These findings make one realize that the prognosis in children with convulsions is not too favorable.

HIGGINS, Boston.

DIAGNOSTIC CHARACTERISTICS OF USE FOR DETERMINING THE PARTICULAR TYPE OF EPILEPTIC OR NONEPILEPTIC SEIZURES OF A CHILD. M. L. GROSSI-BIANCHI and F. M. PISTONE, Minerva pediat. 7:224 (Feb. 24) 1955.

The differential diagnosis of the various types of convulsions and epileptic seizures is discussed in detail. It must be remembered that the anticonvulsive action of the drugs will be different according to the presence and nature of organic cerebral lesions. From a group of 357 epileptic children, 46% of the grand mal cases, 22% of the petit mal cases, 46% of the skinetic cases, 32% of the myoclonic cases, and 34% of the psychomoter cases had evident cerebral lesions.

HIGGINS, Boston.

THE TREATMENT OF CHOREA MINOR WITH INSULIN. E. PENNATI, Minerva pediat. 7:523 (April 21) 1955.

Eleven children with chorea were given daily small doses of insulin (5 units t.i.d.).

The period of activity in nine of these children was reduced from the usual period of 40-60 days to 25-30 days. Each child showed a gain in weight in this period. The medication was observed to overcome the usual tendency to muscular atonia.

HIGGINS, Boston.

SULPHONAMIDES AND ANTIBIOTICS IN THE TREATMENT OF MENINGITIS DUE TO THE PNEUMOCOCCUS OR TO THE BACILLUS OF PFEIFFER. A. CROSCA and G. PARRINELLO, Pediatria 62:58 (Jan.) 1954.

There have been treated at the Pediatric Clinic of Messina over a four-year period (1949-1953) 32 cases of pneumococcus meningitis, with 18 recoveries, and 10 cases of influenza meningitis, with 8 recoveries. With each type, a combination of penicillin and streptomycin therapy proved the most satisfactory. Aureomycin was also found to be very efficacious in the pneumococcus cases. The prognosis was much poorer in the cases secondary to an otitis media and when treatment was started late in the disease.

HIGGINS, Boston.

PSEUDOTUMORAL SEROUS MENINGITIS WITH AMAUROSIS AND RAPID RECOVERY. GIAMPAOLO GELLI, Riv. clin. pediat. 53:173 (Feb.) 1954.

After describing the different conditions which may produce the pseudotumoral syndrome, the author reports in detail a case of serous meningitis in a 4-year-old girl whose symptoms of grave endocranial hypertension were followed within only three days by a nearly complete amaurosis.

Skull trepanation and following cortisone treatment produced a complete and durable recovery within a few days. An allergic pathogenesis may be probable, and this opinion is supported.

FROM THE AUTHOR'S SUMMARY

RECENT KNOWLEDGE ABOUT POLIOMYELITIS. AUGUSTIN ARRIAGADA, Acta pediat. españ. 13: 1-12 (Jan.) 1955.

The author points out that the various strains of virus which cause poliomyelitis produce immunity only for the specific strain. The virus of any given strain can be carried by healthy persons with no sign of illness.

There are also subclinical types of illness not easily recognized. In any case of recognizable poliomyelitis the virus should be searched for in the feces, and antibodies may be found in the blood of healthy carriers and in persons with the subclinical form of the disease.

The author discusses the various forms poliomyelitis may take and gives some of his personal experiences in his home country, Chile.

The different types of poliomyelitis may be described as (1) the silent, with all clinical symptoms confined to the intestinal tract; (2) the abortive form, in which the gastrointestinal illness is present and a viremia but no paralysis; (3) a nonparalytic form in which there may be central nervous system involvement but no clinical paralysis and no intestinal involvement; (4) the paralytic form.

He discussed the possibilities of hosts for the virus between epidemics; the possibility of fungus and/or saprophytes as the host, and the role of allergy to the disease.

Finally, he compares the acute poliomyelitis with multiple sclerosis.

ALLEN, Santa Fe, N. Mex.

INCIDENCE OF POLIOMYELITIS IN CHILDREN WITH SPASTIC CEREBRAL PALSY. EMILIO R. VIGIL LORENZO, Acta pediat. españ. 13:256-259 (April) 1955.

The author presents case histories of three children with poliomyelitis who had cerebral palsy. Two cases were attributed to prematurity and the third to asphyxia neonatorum.

In the first there was the curious observation of flaccid paralysis in one lower extremity and spastic in the other.

In the second case there was very notable contrast between the hypotonicity of the lower extremities with the rigidity of the upper extremities and the massive rigidity of the back muscles.

The third child had flaccid right leg and a certain amount of rigidity of all of the rest of her muscles.

The author does not believe such things are as exceptional as once believed and that it is an indication of the fragility and vulnerability of the nervous system in these children.

ALLEN, Santa Fe, N. Mex.

CONVULSIONS IN CHILDREN SUFFERING FROM MONGOLISM. M. SCHACTER, Acta pediat. españ. 13:311-314 (May) 1955.

The author feels that better statistical studies should be made before stating that convulsions among Mongoloid children are rare. He cites several authors who have made this statement and gives some statistics of his own in his capacity as consultant to the committee on mental deficiency in children at Marseilles.

ALLEN, Santa Fe, N. Mex.

A STUDY OF SOME ETIOLOGICAL FACTORS OF CONGENITAL ENCEPHALOPATHY. A. BALLABRIGA, Arch. pediat., Barcelona 5:411-458 (Jan.-Feb.) 1955.

In this section of his study of encephalopathies of a congenital or hereditary nature, Dr. Ballabriga confines himself to (1) nuclear icterus lesions due to isoimmunization and those not due to any erythroblastotic process and (2) those lesions of the nervous system which develop as a result of malformations in adjacent structures.

In this last group there are a wide variety of conditions, such as anencephaly, microcephaly, hydromanencephaly, and hydrocephaly. He illustrates with numerous photographs of these deformities, clinical histories, and the possibility of treatment in hydrocephaly. Air encephalograms and ventriculograms are shown for certain of the cases.

He has made a very extensive study of the literature on encephalopathies, with a very full bibliography classified as to subject matter.

ALLEN, Santa Fe, N. Mex.

INTRACRANIAL SURGICAL VASCULAR AFFECTIONS IN CHILDHOOD. MARCO MALDONADO, HECTOR VALLADARES, and REINALDO POBLETTE, Rev. chilena pediat. 25:5 (Jan.) 1954.

The authors report two cases of spontaneous intracranial hemorrhage in children 10 and 9 years old who recovered after surgical treatment. In one case the abrupt onset of the hemorrhage corresponded to an arteriovenous aneurysm, while the second case, with repeated small hemorrhages, corresponded to a vestigial, arterious aneurysm.

If one suspects the presence of an intracranial aneurysm, arteriography must be done immediately, an innocuous procedure that will confirm the diagnosis and together with the clinical symptoms will exclude any differential diagnosis. Surgical treatment must be immediately resorted to, because even if it is true that some aneurysms are reported to have cured spontaneously by fibrosis, these cases are exceptional, and the general rule is that if these cases are not operated on they die due to repeated hemorrhage. There are many causes for spontaneous intracranial bleeding in childhood, but probably the most frequent one is an intracranial aneurysm, which is commoner than the few reports in the literature would lead one to suspect.

FROM THE AUTHORS' SUMMARY.

Diseases of Genitourinary Tract

ABNORMALITIES OF SCROTAL CONTENTS IN CHILDREN. DONALD A. CHARNOCK, California Med. 80:62 (Feb.) 1954.

Disorders of the scrotal contents in infancy and childhood parallel fairly closely those found in adults and deserve equal consideration. Hydroceles, epididymitis, hernia, and cryptorchism are the commoner conditions; but injuries, torsion of the spermatic cord, and malignant tumors also occur in this age group.

Early, accurate diagnosis and definitive treatment increase the prospect of children with testicular disease developing into healthy, fertile adults.

PRYOR, Redwood City, Calif.

A CONTROLLED INVESTIGATION OF THE EFFECT OF DIET ON ACUTE NEPHRITIS. R. S. ILLINGWORTH, M. G. PHILPOTT, and JOHN RENDLE-SHORT, Arch. Dis. Childhood 29:551 (Dec.) 1954.

Forty-two children aged from 2 to 14 years, suffering from acute nephritis, were allocated by the random-sampling method to one of two dietary regimens—severe protein

restriction and the normal ward diet. No case was observed for less than a year; the average period of observation was over two and a half years. The two groups were shown to be statistically comparable. Strict criteria for "healing" were laid down.

There was one death in the low-protein group. In the remaining children no significant difference in the rate of healing was observed.

The authors were unable to demonstrate any advantage in protein restriction.

KELLY, Milwaukee.

NEW DYSMETABOLIC AND DYSENDOCRINE SYNDROME: IDOPATHIC RENAL ACIDOSIS WITH NEPHROCALCINOSIS AND HYPOPOTASSEMIC PSEUDOPARALYSIS, NANISM, LATE RICKETTS, AND ADIPOSOGENITAL DYSTROPHY. G. DE TONI, Ann. Paediat. 182:63 (Feb.) 1954.

The author presents the history of a boy who at 7 months of age showed a transitory polyuria with polydipsia; these phenomena became chronic after the second year of life. At about the ninth year polyphagia, obesity, hypogenitalism, genu valgum, retardation of body growth, and muscular asthenia with hypokalemia and transitory muscular pseudoparalysis appeared. The clinical examination revealed an osteoporosis with symptoms of late rachitis, nephrocalcinosis, large urinary bladder, polyuria with isosthenuria and alkaline or neutral urine, an extraordinary calciuria, and a disorder of the elctrolytes (low alkaline reserve, low natremia and phosphatemia, high chloremia). Alkaline treatment, as prescribed by Albright, brought recovery of the muscular asthenia and resumption of statural growth, but the alkaline reserve is still low, and the urine is always neutral or alkaline. The author ascribes the dysmetabolic and dysendocrine syndrome referred to above to idiopathic renal acidosis of congenital origin. The connection between the idiopathic renal acidosis and the nephrocalcinosis, the muscular asthenia with pseudoparalysis of hypopotassemic type, the nanism, and the late rickets is easy to show. In fact, even the adiposity, according to the author, should in this case be attributed to a renal origin. In support of this hypothesis he alludes to several cases in the literature in which adiposity and adiposo-genital syndromes are described in connection with chronic kidney disorders. Consequent on such an assumption, a new chapter, in addition to those on renal nanism and renal cachexia, will have to find a place in the field of growth pathology —renal adiposity.

FROM THE AUTHOR'S SUMMARY

FURTHER OBSERVATIONS ON "CYSTINOSIS." E. FREUDENBERG, Ann. paediat. 182:85 (Feb.) 1954.

Description of a case of cystinosis, with inhibition of growth, chronic amino-aciduria, severe vitamin-D-resistant rickets, and deposit of cystine in the bone marrow and the cornea is presented.

The discovery is new that the bone marrow also contains an accumulation of tyrosine, identified by tyrosinase. Analogous findings were made in cuts from lymph nodes and bone marrow in several other cases.

Aklali treatment and choline did not give any therapeutic success in this case. Yeast adenylic acid, 50 mg. daily, got rid of the glycosuria, cured the rickets (although the rate of inorganic phosphorus remained low), and markedly reduced the amino-aciduria, without abolishing it completely. The amount of neutral sulfur in relation to total sulfur was reduced, while the oxydized sulfur was increased. Brand's test, however, remained positive, and cystine could still be shown to be present in the urine by the chromatographic method. The possible effect of the absence of certain phosphate combinations in the pathogenesis of cystinosis is pointed out.

FROM THE AUTHOR'S SUMMARY

SEVERAL KIDNEY DISEASES AND SCHOENLEIN-HENOCH'S SYNDROME. ALFREDO U. RAMON GUERRA, CARLOS A. ESCANDE, JOSE M. PORTILLO, CARLOS A. BAUZA, and CARLOS BOCCOLERI, Arch. pediat. Uruguay 25:22 (Jan) 1954.

Of 23 cases of Schönlein-Henoch's syndrome, 8 were found with glomerular nephritis —1 of superacute course, 2 subacute, and 5 subchronic or chronic. The previous observations were confirmed as to some characteristics of its course (frequently of nonrecovery) and of its clinical aspects (repeated hematuria). The classical treatment with penicillin and streptomycin and that with synthetic antihistamine drugs was ineffective in this series. The action of cortisone, even if it appeared favorable in some aspects, could not be confirmed,

especially in relation to urinary symptoms. The treatment with penicillin-streptomycin was carried out in normal doses. The possibility is considered of using massive doses, such as used in bacterial endocarditis. Finally, the history and the actual conception of the syndrome is reviewed, suggesting the hypothesis that it may be the infantile or juvenile, generally reversible, form of periarteritis nodosa, which would be, especially in the adult form, irreversible.

FROM THE AUTHORS' SUMMARY

SALT AND WATER METABOLISM AND ITS PREDOMINANT SIGNIFICANCE IN THE TREATMENT OF UREMIA IN CHILDHOOD. WERNER DROESE and HELGA STOLLEY, Deutsche med. Wchnschr. 79:1599 (Oct. 22) 1954.

Death in uremia is mainly due to a faulty concentration of ions and not to an intoxication by degradation products of protein. Until restoration of the renal function, the aim of therapy is the restoration of the fluid volume and the normal ionic composition of the body fluids. It is guided by repeated determination of sodium, chlorine, and bicarbonate of blood (i. e., serum or plasma) and by careful determination of the body weight, allowing the calculation of the total ionic concentration of the organism with partition in extra cellular and intracellular compartments as well as deficits or excess of body water. The calculation follows that of Darrow and Yannet. The treatment of uremia in the course of acute and chronic glomerulonephritis and in necrotizing nephrosis (lower nephron nephrosis) is discussed, with attention to the danger of administering too much or too little water, as well as salts. Cardiocirculatory disorders, as well as infections, demand special treatment. The diet of the patients in uremia, as well as in reconvalescence, is discussed.

AMBERG, Rochester, Minn.

INVOLUNTARY URINARY EXCRETION AND DYSTOPIC URETERAL OUTLETS. G.-H. KÖTZCHKE, Deutsche med. Wchnschr. 80:210 (Feb. 11) 1955.

The diagnosis of involuntary urine excretion is discussed, and two cases are reported. A 12-year-old girl was always wet. A duplication of both kidneys and ureters was found, with a displacement of the opening of each of one pair of ureters. A 16-year-old girl had been submitted to psychotherapy for incontinence. On one side a double renal pelvis was found with double ureters, one of which with displaced opening. Both conditions yieled to surgical correction.

AMBERG, Rochester, Minn.

TREATMENT OF NEPHROTIC SYNDROME WITH ACTH. I. A. MOCHTAR and O. M. DE VAAL, Maansschr. kindergeneesk. 22:20 (Jan.) 1954.

The results obtained with ACTH in the treatment of seven children suffering from the nephrotic syndrome are described. Sometimes it is possible to produce a remission with fairly large doses, but no real therapeutic successes were seen. In one case, steroid diabetes developed. Two hypotheses concerning the mechanism of the action of ACTH are mentioned.

FROM THE AUTHORS' SUMMARY.

BIOPHYSICAL AND CHEMICAL INVESTIGATION ON BONE TISSUE IN EXPERIMENTAL HYPERPARATHYROIDISM. BENGT ENGFELDT and ROLF ZETTERSTRÖM, Endocrinology 54:506 (May) 1954.

There have been considerable differences of opinion concerning the mode of action of the parathyroid hormone on bone tissue. The discussion of this problem has followed two main lines, one school holding that the effects of the hormone are secondary to an increased excretion of phosphate in the urine and the consequent lowering of the phosphate level in the blood, and the other school maintaining that the parathyroid hormone exerts a direct action which causes bone resorption.

It was the aim of the present investigation to obtain some further information concerning the reaction of bone tissue in experimental hyperparathyroidism using biophysical and chemical methods along with the usual morphological ones.

The effects of parathyroid hormone on bone tissue were investigated by studying the rate of renewal of bone phosphate, using chemical and autoradiographic techniques, and the general distribution of mineral salts, using microradiography. In young animals the rate of renewal of bone phosphate is decreased but is increased in the case of old animals.

The destruction of bone tissue is accelerated by the parathyroid hormone, but the characteristics of the process are unchanged.

The detailed mechanism of the parathyroid action on bone remains obscure, but there are several pieces of indirect evidence favoring the theory that a primary action of the hormone on an organic constituent of bone tissue takes place.

JACOBSEN, Buffalo.

Diseases of Ductless Glands; Endocrinology

HISTOPHYSIOLOGICAL STUDY OF THE DEVELOPING ADRENAL CORTEX OF THE RAT DURING FETAL AND EARLY POSTNATAL STAGES. JOHN B. JOSIMOVICH, AARON J. LADMAN, and HELEN WENDLER DEANE, Endocrinology 54:627 (June) 1954.

The histochemical and morphological evidence indicates that active secretion by the cortical cells occurs at least after 19½ days of gestation and, further, that activity diminishes immediately after birth.

JACOBSEN, Buffalo.

ANTERIOR PITUITARY GROWTH HORMONE ADMINISTRATION IN B VITAMIN DEFICIENCIES IN THE RAT. J. L. BEARE, J. R. BEATON, and E. W. MCHENRY, Endocrinology 55:40 (July) 1954.

Rats deprived of pyridoxine, pantothenic acid, or riboflavin cannot respond to the growth hormone.

JACOBSEN, Buffalo.

SIMULTANEOUS RELATIVE HYPER- AND HYPO-CORTICOIDISM IN DIFFERENT REGIONS OF THE SAME INDIVIDUAL. HANS SELYE, Endocrinology 55:105 (July) 1954.

Earlier investigations gradually led the author to the concept that an important factor in the pathogenesis of many diseases is the failure to adjust the blood corticoid level to the special requirements created by the evocative pathogen. Maladies in which such an inadequate adjustment of corticoid secretion is the decisive factor were thought to represent an important group among the "diseases of adaptation." However, this hypothesis is difficult to reconcile with the fact that, by all available assay methods, the corticoid concentration in blood and in urine may be virtually normal in a variety of inflammatory conditions which were considered to be diseases of adaptation.

It is also apparently incompatible with such a humoral concept of pathogenesis that lesions which had been ascribed respectively to hypocorticoidism or hypercorticoidism may be present simultaneously in the same person, for instance, in a patient with concurrent rheumatoid arthritis and active pulmonary tuberculosis. Here, the inflammation around the joints is excessive, and antiphlogistic therapeutic measures are advantageous, while in the lung, the development of the inflammatory granulomatous barricade is manifestly insufficient to protect the patient against the spread of the microbes.

The object of this communication is to report upon a series of recent experiments designed to clarify this problem in two ways. Firstly, the experiments were done to verify, under varied conditions, whether or not the necrosis-producing effect of a given local stressor can be enhanced, while its ability to cause inflammation is simultaneously depressed, by an antiphlogistic corticoid. Secondly, they were done to furnish concrete experimental proof that, under suitable conditions, a relatively hypercorticoidism and hypocorticoidism can coexist in different regions of the same animal organism.

Using a "double granuloma-pouch" technique, one test area of connective tissue was rendered relatively resistant by pretreatment with small doses of croton oil, and then a high concentration of this same irritant was introduced into both areas.

Control rats not hormone treated responded only with strong inflammation in both areas. The response was markedly altered, however, in rats which received daily treatment with hydrocortisone. In the pouches which had not been protected by pretreatment with the low concentration of croton oil, the subsequently applied stronger solution produced inflammation and exudation in the controls, while in the rats receiving Cortisol, necrosis ensued. Thus, it became possible to induce a relative hypercorticoidism and hypocorticoidism simultaneously in different regions of the same animal, in that a given dose of hydrocortisone proved insufficient to suppress the lesions completely in one focus, although it actually aggravated them in an adjacent area.

JACOBSEN, Buffalo.

CYTOLOGICAL DEMONSTRATION OF NORADRENALINE IN THE SUPRARENAL MEDULLA UNDER CONDITIONS OF VARIED SECRETORY ACTIVITY. NILS-AKE HILLARP and BERNT HOKFELT, Endocrinology 55:255 (Sept.) 1954.

Oxidation of arterenol in vitro with potassium iodate gives a selective pigment formation, making possible differentiation from epinephrine. When applied cytologically to the adrenal medulla this reaction of pigment formation suggested that arterenol is stored within special medullary cells. These investigations, however, did not exclude the possibility that the "arterenol cells" are nonspecific, representing only varying degrees of secretory activity in the medulla.

Using the above method for the cytological demonstration of arterenol, the authors studied the adrenal medulla under different conditions of secretory activity.

Evidence has been put forward to show the existence of specific "arterenol cell complexes" within the adrenal medulla. This is strongly supported by the fact that in the cat and in the rat insulin-induced hypoglycemia, which causes a gradual depletion of the epenephrine content of the adrenal gland without any decrease of the arterenol content, does not alter either the number of the arterenol pigment-forming cells or the intensity of the pigment reaction.

The cytological findings described in this paper are in agreement with the physiological view that arterenol and epinephrine are two specific hormones which are selectively secreted from the adrenal medulla under different conditions.

JACOBSEN, Buffalo.

ENDOCRINE FACTORS IN THE RESPONSE OF THE HYPOTHROID RAT TO COLD. HENRY H. FREEDMAN and ALBERT S. GORDON, Endocrinology 56:135-142 (Feb.) 1955.

Following either thyroidectomy or adrenalectomy the rat fails to survive exposure to conditions of low environmental temperature that are tolerated indefinitely by the intact animal.

The experiments reported herein were undertaken to determine whether the pituitary-adrenocortical axis of the hypothyroid rat can respond to physiological stress (e.g., cold) and, if so, whether the response is abnormal.

The evidence from the experiments reported strongly supports the view that there is no incompetency of the pituitary-adrenocortical axis in the hypothyroid rat in cold.

JACOBSEN, Buffalo.

THE RESPONSE OF THE PITUITARY-THYROID SYSTEM OF THE GUINEA PIG TO LOW ENVIRONMENTAL TEMPERATURE. C. E. STEVENS, S. A. D'ANGELO, K. E. PASCHKIS, A. CANTAROW, and F. WILLIAM SUNDERMAN, Endocrinology 56:143-156 (Feb.) 1955.

Although the influence of low environmental temperature on the functional activity of the thyroid gland has engaged the attention of many investigators, in only a few studies has the interplay of the pituitary-thyroid system in cold exposed animals been assessed by functional criteria in both glands.

In the present work the relationship between the histophysiologic changes in the thyroid and the adenohypophysis and their relation to the peripheral tissues have been investigated in the cold-exposed guinea pig by measurements of the basal metabolic rate, the serum protein-bound iodine, the I^{131} uptake and release by the thyroid gland, the thyrotrophic hormone levels in the blood and anterior pituitary, and the evaluation of the histocytology of the thyroid and adenohypophysis. The results are considered to indicate that exposure of the guinea pig to low environmental temperature causes an activation of the pituitary-thyroid system, involving increased rates of thyrotrophic and thyroid hormone secretion, which accounts largely for the increased oxidative metabolism in cold.

JACOBSEN, Buffalo.

BLOOD ACTH IN THE STRESSED ADRENALECTOMIZED RAT AFTER INTRAVENOUS INJECTION OF HYDROCORTISONE. KATHERINE L. SYDNOR, Endocrinology 56:204-208 (Feb.) 1955.

It is known that the secretory products of the adrenal cortex inhibit ACTH release in the intact rat. Estimations of alterations in the rate of secretion of ACTH were based on changes in weight or the concentration of ascorbic acid of the adrenal glands of the test animal. These indices limit the evaluation of pituitary control, since the response in the target gland is measured hours or days after steroid administration. The development of a technique for measuring ACTH in blood has made it possible to study ACTH release in

the adrenalectomized animal within a few minutes after administration of hydrocortisone.

From experiments in which this new method was used, it is concluded that (1) intravenously administered hydrocortisone can effectively block ACTH release in the stressed adrenalectomized rat within one to two minutes and (2) a high concentration of hydrocortisone in blood will not interfere with the recovery of ACTH.

JACOBSEN, Buffalo.

A RELATIONSHIP BETWEEN VITAMIN A METABOLISM AND CORTISONE. I. CLARK and R. W. COLBURN, Endocrinology 56:232-238 (March) 1955.

During the course of investigations concerning the effect of cortisone upon lipid metabolism, it was observed that the color of the lipid extracts of the liver from cortisone treated rats were usually less yellow than their controls. Carotenoid pigments contribute color to the lipid solvent extracts of liver, and since B-carotene is the precursor of vitamin A, it was decided to investigate what effect, if any, cortisone might have upon vitamin A metabolism.

The experiments here reported indicate that a relationship between the adrenal steroid cortisone and vitamin A metabolism does exist.

JACOBSEN, Buffalo.

THE EFFECT OF GROWTH HORMONE AND THYROXINE ON THE MITOTIC RATE OF THE INTESTINAL MUCOSA OF THE RAT. C. P. LEBLOND and RITA CARRIERE, Endocrinology 56:261-262 (March) 1955.

Since an increase in cell number is one of the processes by which organs and tissues grow, it was of interest to investigate how cellular proliferation is influenced by two major growth-promoting factors, the pituitary growth hormone and the thyroid hormone, thyroxine.

Replacement doses of these two hormones were therefore administered, separately or in combination, to thyroidectomized and/or hypophysectomized rats, and cellular proliferation was investigated by counting the dividing cells in the crypts of Lieberkühn of the duodenum, where under normal conditions mitoses are abundant and appear at a constant rate.

The number of dividing cells in the crypts of Lieberkühn, 8.0% in intact animals, is depressed to 5.0% by thyroidectomy and to 3.9% by hypophysectomy.

Treatment with growth hormone increases the mitotic rate regardless of operative treatment and restores it to, or close to, the normal range.

Thyoxine restores the mitotic rate to normal, but only in the presence of the hypophysis. This effect is believed to be mediated by endogenous growth hormone.

It is suggested that the mitogenic effect of growth hormone may play a role in the growth response of the organism to this hormone.

JACOBSEN, Buffalo.

MODE OF ACTION OF THE HYPERGLYCEMIC-GLYCOGENOLYTIC FACTOR FROM URINE. FRANCISCO MOYA, Endocrinology 56:312-321 (March) 1955.

The hyperglycemic and glycogenolytic properties of a urinary extract have been shown to be due partially, if not entirely, to the presence of a factor other than pancreatic glucagon. Further, this urinary preparation was found to stimulate glycogenolysis by liver homogenates, a property not shared by either glucagon or epinephrine. The present study was undertaken in an attempt to determine the site of action of the urinary factor in the chain of enzymatic reactions leading from liver glycogen to glucose. The experiments reported show that this factor contains an amylase which accounts for at least part of its glycogenolytic activity.

JACOBSEN, Buffalo.

STEROID DIABETES IN GUINEA PIGS: EFFECTS OF HYDROCORTISONE ADMINISTRATION ON BLOOD AND URINARY GLUCOSE, NITROGEN EXCRETION, FAT DEPOSITION, AND THE ISLETS OF LANGERHANS. FRANZ X. HAUSBERGER and ANDREW J. RAMSAY, Endocrinology 56: 533-540 (May) 1955.

Cortisone administration to guinea pigs with free access to food produces effects resembling in many respects Cushing's syndrome in man. The purpose of this study was to investigate the influence of hydrocortisone administration in guinea pigs. This steroid induces similar metabolic changes but the effects on body weight and nitrogen excretion are more marked than those produced by cortisone.

JACOBSEN, Buffalo

EFFECTS OF RENIN IN RATS TREATED WITH METHYLANDROSTENEDIOL. G. M. C. MASSON, EDWARD R. FISHER, A. C. CORCORAN, and IRVINE H. PAGE, Endocrinology 56:541-546 (May) 1955.

Methylandrostenediol is shown to elicit hypertension and hypertensive vascular lesions in uninephrectomized, salt-fed rats. This hypertensive state resembles the type of hypertension produced by injections of anterior pituitary extracts; both are associated with degenerative changes in the adrenals.

The mechanism of methylandrostenediol hypertension is distinct from that of DCA hypertension. It may represent an indirect response, possibly mediated by renin, to the stimulus of excessive renal growth.

JACOBSEN, Buffalo.

STUDIES OF 17-HYDROXYCORTICOSTEROIDS. ALAN K. DONE, ROBERT S. ELY, and VINCENT C. KELLEY, J. Pediat. 44:153 (Feb.) 1954.

The authors start with the premise that salicylates may, in high doses, influence the pituitary-adrenal system and its secretions. They have reported, before this, elevated plasma 17-hydroxycorticosteroid in a child with salicylate intoxication. Now they report elevation of 17-hydroxycorticosteroid in the plasma of seven patients with salicylate intoxication. They say that the steroids are also elevated in guinea pigs given large doses of sodium salicylate intraperitoneally.

MACDONALD, Pittsburgh.

STUDIES OF 17-HYDROXYCORTICOSTEROIDS: IV. EVALUATION OF A STANDARD ACTH-17-HYDROXYCORTICOSTEROID RESPONSE TEST IN CHILDREN, ROBERT S. ELY, RICHARD B. RAILE, PATRICK F. BRAY, and VINCENT G. KELLEY, Pediatrics 13:403 (May) 1954.

An ACTH-17-hydroxycorticosteroid response test is described as a measure of adrenal cortical function in which the change in plasma concentrations of 17-hydroxycorticosteroids in response to the intramuscular injection of 25 international units of ACTH is determined.

The limitations of this test are discussed, and it is compared with other tests of adrenocortical function.

No correlation is seen between the magnitude of steroid elevation and of eosinopenia in response to ACTH. These data suggest that the ACTH-induced eosinopeina is not mediated by elevations in the circulating concentrations of 17-hydroxycorticosteroids.

Although this test might be improved by modifying the ACTH dose or route of ACTH administration, the direct measurement of alterations in circulating concentrations of 17-hydroxycorticosteroids probably represents the most practical approach to evaluation of adrenocortical responsiveness.

FROM THE AUTHORS' SUMMARY.

NEUROBLASTOMA OF THE SUPRARENAL GLANDS. M. V. SIRSAT, Indian J. Child Health 3:1 (Jan.) 1954.

Pathological studies of four cases of adrenal neuroblastoma are presented. Neuroblastoma is considered fairly rare, these cases having occurred over a 10-year period.

MCGUIGAN, Evanston, Ill.

THE USE OF TESTOSTERONE IN CHILDREN. GERARD-LEFEBVRE, BERNARD-GAUDIER, and R. JACQUEMONT, Pédiatrie 10:227, 1955.

After discussing the biological action of testosterone, its specificity, and metabolic effects and dosage in children, the authors discuss the indications (growth retardation, dwarfism, prematurity, asthma, cardiac malformations leading to physical retardation, kidney disturbances, hypervitaminosis D_2, ossification disturbances, endocrine disturbances, as antidote to cortisone's side-effects, Mongolism, genital insufficiency of the adolescent) and contraindications (underlying infections and male hypergenitalism).

Caution is indicated with regard to dosage in conditions of questionable response, such as cryptorchism and gynecomastia and in its use in the female.

GLASER, Baltimore.

STUDIES IN DIABETES MELLITUS. GUNNAR ENGLESON, Acta pædiat. Vol. 43 Supp. 97 (May) 1954.

Factors considered of primary importance in the development of late complications of diabetes were studied in a series of 217 adult patients, treated at the medical department of

the Växjö Hospital, and in a childhood series consisting of 42 juvenile diabetics, treated at the pediatric department of the University of Lund. Both series were on a free diet.

Attention was directed mainly to the importance of diet and to problems bearing on liver metabolism and endocrine function, and the results are accounted for against the background of literature studies of earlier investigation in this field.

The observations of interest may be summarized as follows: 1. Of the Växjö series, which consisted of patients in whom diabetes had occurred before the age of 40 years, the following late complications were noted after 5 to 25 years of duration of diabetes: nephropathy in 65%, retinopathy in 60%, and hypertension in 65% of the cases. Nephropathy was practically always the first of these late symptoms to appear. Of the patients who had had diabetes for more than 10 years, only seven (6.5%) were free of vascular complications.

The Kimmelstiel-Wilson syndrome was diagnosed on clinical grounds in 24 cases, and in one-third of the cases the diagnosis was confirmed post mortem. The serum hexosamine was often found to be increased, especially in the presence of vascular lesions.

2. Of the Lund series (19 boys and 23 girls) the liver parenchyma was found to be involved in 40% of the cases. It is typical of these liver complications that they appear about five years after the onset of diabetes, that they are fairly often seen (about 30% of the time) in combination with moderate retardation of growth, and that they are sometimes seen (about 20% of the time) with coexistent or subsequent vascular complications in the form of nephropathy and/or retinopathy.

Endocrine function studies in the Lund series suggested that a primary endocrine non-pancreatogenic form of diabetes is rare and that the functional patterns of the adrenal cortex during ketosis or "stressful life situations" readily change.

The observations described above suggest the following conclusions: 1. The development of long-term diabetes is influenced not only by duration of the diabetes but also by any impairment of liver function and by endocrine factors, probably mediated via the adrenohypophyseal axis and by stressful life situations.

2. The disturbed liver function and endocrine homeostasis of the body is ascribable to, or at least favored by, unrestricted diet.

3. Dietary restrictions should be observed in the management of diabetes, especially as a prophylactic measure against long-term diabetes.

FROM THE AUTHOR'S SUMMARY

Diseases of Muscles, Bones, Joints, and Lymph Nodes

INFANTILE CORTICAL HYPEROSTOSIS. JAMES B. SIDBURY JR. and J. BUREN SIDBURY, New England J. Med. 250:309 (Feb.) 1954.

The syndrome that has become known as infantile cortical hyperostosis, after the suggestion of Caffey and Silverman, is characterized by the usually sudden onset of swelling of the face, thorax, or extremities, hyperirritability, fever, fluctuating course, and roentgenographic evidence of periosteal new bone formation.

The cause of this disorder is not entirely established. It occurs almost exclusively in infants under 5 months of age, affecting boys and girls equally. Increasing evidence is accumulating that suggests some intrauterine or genetic factor, and the authors give arguments supporting this hypothesis.

The pathology is described, and the role of hypoxia is delineated as the possible source of the hyperplasia of the periosteum, which is responsible for the overproduction of imperfect bone. It is suggested that arterial intimal proliferation is the cause of the hypoxia and is an inherited defect.

The authors present in detail 10 cases of infantile cortical hyperostosis. The average age before complete subsidence of all symptoms and signs was 9½ months; in four cases, 27 months elapsed before all x-ray evidence of the disease had disappeared.

The criteria for diagnosis, the differential diagnosis, and the use of cortisone as a means of shortening the course and reducing the danger of suffocation from pharyngeal edema are given.

The syndrome is commoner than is generally appreciated.

WHEELOCK, Denver.

CONGENITAL BOWING AND ANGULATION OF LONG BONES. CAROL R. ANGLE, Pediatrics 13:275 (March) 1954.

The clinical picture of congenital angulation and bowing of the long bones is presented, and 37 roentgenographically proved cases are reviewed from the English literature. A case of bilateral femoral angulation is presented. The pathogenesis of the condition is discussed and correlated with mechanical principles and with the published results of experimental investigations. It is concluded that although the etiology is still uncertain, the mechanical theory is most acceptable. Some modifications of this theory are offered.

FROM THE AUTHOR'S SUMMARY

ANEURYSMAL BONE CYSTS. DAVID C. DAHLIN, BYRON E. BESSE JR., DAVID G. PUGH, and RALPH K. GHORMLEY, Radiology 64:56-65, 1955.

Aneurysmal bone cyst is described as a distinct and pathological entity, supporting the opinion of Jaffe and Lichtenstein (1942). Ewing, in 1940, had employed the term "aneurysmal-giant-cell tumor." The authors' report is based upon their findings in 26 cases, 11 of which were under 15 years of age. Most of the bones of the trunk and extremities are subject to involvement, but principally the vertebra and long bones.

In two-thirds of the cases this tumor exhibited a characteristic roentgenographic picture. There was a well-circumscribed rarified area, usually occupying an eccentric position in bone, which showed either fine or coarse trabeculae, or both. The trabeculae were more coarse and more numerous toward the edge of the lesion, producing a soap-bubble or honeycombed appearance. The cortex bulged eccentrically or was absent at the periphery; frequently only irregular remnants remained. Lesions of the small bones were often found to bulge symmetrically in a fusiform fashion. The size of the cyst was found to be in direct proportion to its duration.

In long bones the end of the shaft was the site of predilection. If endochondral bone growth was still taking place, the cyst was always on the diaphyseal side of the epiphyseal cartilage.

In the spinal column only a part of a vertebral body was involved, with extension of the lesion to the pedicle, lamina, and transverse process.

The gross and microscopic pathologic appearance was typical in all cases. In the past, the preoperative diagnosis has varied from simple bone cyst to osteogenic saccoma, almost never aneurysmal bone cyst.

ANSPACH, Riverside, Ill.

EARLY DIAGNOSIS OF CONGENITAL DISLOCATION OF THE HIP. W. FRISCHKNECHT and S. GALLEN, Helvet. paediat. acta 9:43 (April) 1954.

Congenital dislocation of the hip must be diagnosed as early as possible so that early treatment can achieve its aims, the prevention or at least the speedy reduction of the dislocation in the hip joint and the diminution of regressive changes in the affected joint. The so-called dislocation phenomenon should be systematically sought in the newborn before the age of 2 or 3 weeks. In older infants a possible abduction defect should be investigated at every physical examination. From the age of 4 months the diagnosis can very often be made by x-rays.

A report on four cases from the author's practice is presented: three female siblings, including a pair of uniovular twins, were all suffering from bilateral hip dislocation. The diagnosis was verified by x-rays at 5, 9, and 20 months, respectively. In the fourth case there was unilateral congenital hip dislocation associated with bilateral cleft palate.

FROM THE AUTHORS' SUMMARY.

PERIOSTEAL BONE DEPOSITS AS EXPRESSION OF A DISTURBANCE OF CALCIUM METABOLISM. R. SEYSS and E. WIESNER, Helvet. paediat. acta 9:59 (April) 1954.

A case of a centrally caused (abacterial meningitis) disturbance of the calcium metabolism (double contour of the femur) in a 9-week-old infant with severe tonic-clonic convulsions is reported.

FROM THE AUTHORS' SUMMARY.

RHEUMATIC SYNDROME WITH GENERALIZED AFFLICTION OF CARTILAGE. H. HARDERS, Schweiz. med. Wchnschr. 84:712 (June 26) 1954.

Two cases from the literature are reviewed, and a new case is described. The first

patient was a boy 14 years of age; the second, a Negro woman 34 years of age, and the author's, a boy 16 years of age. The disease starts with a catarrhal inflammation of the upper respiratory passages and is characterized by inflammation and softening of the cartilages. In addition, a polyarticular rheumatic syndrome with myocarditis becomes manifest, with episcleritis and iridocyclitis. The changes of the cartilage of the larynx and trachea demand an early tracheotomy. Chronic tracheobronchitis supervenes. In the author's patient, repeated pneumothorax, changing sides, occurred. Softening of the nasal cartilage results in a saddle nose. The term "panchondritis" is proposed.

AMBERG, Rochester, Minn.

HODGKIN'S DISEASE IN CHILDREN. JORGE E. HOWARD and SERGIO JARPA YANEZ, Rev. chilena pediat. 25:205 (May) 1954.

The authors report on 35 cases of Hodgkin's disease in children under 15 years old, seen between the years 1935 and 1952, in which they study the clinical course of the disease. The significance of the blood sedimentation rate, hemogram, and lymph node biopsy is analyzed. The authors were unable to obtain valid correlation between the first two examinations and stated that the surgical biopsy is preferable to the needle biopsy.

They comment on the differential diagnosis, prognosis, and treatment, which varies according to the length of evolution. Their experience permits them to recommend surgical removal of the lymph node and radiotherapy in the early stages. For the advanced cases further treatment with nitrogen mustard, triethylene, melamine, or cortisone and ACTH is advocated.

FROM THE AUTHORS' SUMMARY.

POLYCYSTIC FIBROUS DYSPLASIA (ALBRIGHT'S DISEASE). MIGUEL FIGUEROA and MANUEL NEIRA, Rev. chilena pediat. 25:276 (June) 1954.

A case of polyostotic fibrous dysplasia, or Albright's disease, is described, with its typical signs in the bones and skin. A summary including the clinical characteristics of this condition is added.

FROM THE AUTHORS' SUMMARY.

CHONDROANGIOPATHIA CALCAREA PUNCTATA (CHONDRODYSTROPHIA CALCIFICANS CONGENITA). JENS BERGSTEDT and KARL-HENRIK KARLEN, Monatsschr. Kinderh. 102:347-349 (July) 1954.

The authors report two cases of this rare and atypical form of congenital chondrodystrophy. One infant exhibited at first only the characteristic punctate calcifications at the sites of the navicular, both cuneiform, and the metatarsal bones as well as the greater trochanter of both femora. Later the patient developed a saddle nose. These x-ray findings became less marked as the patient grew. The other infant showed shortening of the left forearm, ulnar deviation on the left, and a shortened left ringfinger. Punctate calcifications were noted on x-ray in the left hand and elbow, sacroiliac region, both feet, and distal sternum.

HARTENSTEIN, Milwaukee.

TREATMENT OF RHEUMATOID ARTHRITIS IN CHILDREN, WITH ACTH AND CORTISONE GIVEN REPEATEDLY. F. KUIPERS, Maandschr. kindergeneesk. 22:109 (April) 1954.

In 12 children severely ill with rheumatoid arthritis (Still's Disease) 26 courses of ACTH or cortisone were given, each lasting between 1 and 10 months (average 3½ months). Also, 11 courses of gold salts and 2 courses of Amidopyrine were given, when renewed signs of activity occurred during or after hormonal therapy. One patient was still under treatment at time of writing. At the last control, between 2 and 36 months after the end of all therapy (average, 14 months), function of joints fell into Class I in two, Class II in seven, Class III in one, and Class IV in one patient, according to the criteria of Steinbrocker, Traeger, and Batterman. Before treatment all patients were bedridden, with one exception, all having signs of active arthritis. At the last control, signs of activity were absent in 10, but the erythrocyte sedimentation rate was higher than 20 mm. after one hour in 5 of these patients. Of paramount importance was the possibility of preventing joint deformities in early cases. In all five patients who entered the clinic during the first 11 months of their illness (Stage I), no deformities occurred, although the diseases progressed to Stage II in three of them. Simple orthopedic measures, such as splinting and traction, together with exercise therapy, proved to be of great value in obtaining these end-results.

Side-effects of the hormonal therapy were slight and reversible. This can only be understood on account of the low dosage of ACTH or cortisone from the very beginning of treatment. Doses of 2 or 3 units of ACTH four times daily or 5 to 10 mg. of cortisone three times daily were usually sufficient to control the signs of activity in such a way that active exercises could be done to prevent or to overcome deformities of the joints.

FROM THE AUTHOR'S SUMMARY

CONGENITAL FISSURE OF STERNUM. J. W. C. DE GROOT and J. C. HUIZENGA, Maandschr. kindergeneesk. 22:203 (June) 1954.

A case of partial sternal fissure is described in a 2-month-old infant, who also had extensive hemangiomatosis. The anatomy and embryology are discussed.

FROM THE AUTHORS' SUMMARY.

Miscellaneous

BLOOD GROUPING TESTS IN DISPUTED PATERNITY PROCEEDINGS. LEON N. SUSSMAN, J. A. M. A. 155:1143 (July) 1954.

A falsely accused man has better than a 50% chance of being excluded as a result of three groups of tests: ABO, M-N, and RhHr.

KIMBALL, Evanston, Ill.

THE INFLUENCE OF CALCIUM, PHOSPHORUS AND VITAMIN D ON THE REMOVAL OF LEAD FROM BLOOD AND BONE. A. E. SOBEL and M. BURGER, J. Biol. Chem. 212:105 (Jan.) 1955.

Young rats were raised on a diet containing 0.8% lead. After a suitable period the administration of lead was stopped and the effect of various diets and vitamin D observed with regard to the lead content of blood and bone.

It was found that a high-calcium-low-phosphorus diet produced the most rapid loss of lead from bone and produced the highest blood level. The addition of vitamin D to the diet caused a decrease in blood lead and a decrease in the loss of lead from bone.

The levels of blood lead and serum phosphorus were such as to suggest a reciprocal relationship.

FORBES, Rochester, N. Y.

CHRONIC LOW-LEVEL EXPOSURES OF YOUNG MICE TO IONIZING RADIATIONS AND THE EFFECT ON FERTILITY. ROBERT RUGH, J. Pediat. 44:248 (March) 1954.

The subjects were mice, male and female, from 2 months to 1 year of age, the normal reproductive period for these animals. The problem was to determine the effect on fertility of weekly injections of radioiodine (NaI^{131})—which emits both β- and γ-radiations but which tends to concentrate in the thyroid gland—and parallel exposures to x-rays of both male and female mice. What is the effect of these agents on mouse fertility? Rugh concludes that β-, γ-, and x-rays are more damaging to the ovary than to the testis, that 10 r x-rays are more deleterious than 4μ of I^{131} given weekly, and that when given at weekly intervals an accumulated dose of 280 r x-rays appeared to be completely sterilizing for the female mouse, whereas 440 r of x-rays over 44 weeks did not appreciably reduce male fertility.

MACDONALD, Pittsburgh.

ERYTHROMYCIN SUSPENSION IN CHILDREN. G. B. GATTMAN and IRVING ROSENBAUM, J. Pediat. 44:547 (May) 1954.

The use of a cinnamon-flavored suspension of erythromycin ethyl carbonate in the treatment of the 31 children with various bacterial infections involving the respiratory tract and middle ear is described. This pediatric preparation was well accepted, showed no toxic side-effects, and was highly effective.

MACDONALD, Pittsburgh.

THE SPEECH CORRECTION FUND: OBJECTIVES, POLICIES AND OPERATING PROCEDURES. HERBERT KOEPP BAKER, SARA STINCHFIELD HAWK, GEORGE A. KOPP, M. D. STEER, ROBERT WEST, and WENDELL JOHNSON, J. Speech & Hearing Disorders 19:258-260 (June) 1954.

The authors report the activities of the Speech Correction Fund of the American Speech and Hearing Association. Scholarships are given to persons studying beyond the master's degree at institutions offering work beyond the master's degree in the field of speech and hearing disorders.

PALMER, Wichita, Kan.

Successful Calcium Disodium Ethylene Diamine Tetra-Acetate Treatment of Lead Poisoning in an Infant. Leighton A. Kneller, Henry S. M. Uhl, and Jacob Brem, New England J. Med. 252:338 (March 3) 1955.

Lead intoxication is a prevalent and important disease with a high morbidity, especially in children.

A case of lead intoxication and encephalopathy in a 20-month-old child is presented, together with clinical and laboratory findings necessary to establish a diagnosis.

A brief outline of the historical treatment of lead poisoning and a commentary on the diagnostic procedures are given. The use of a new therapeutic agent, EDTA (ethylenediamine tetra-acetic acid), or Versene, is discussed. A modified method of administration of the calcium disodium salt useful in pediatrics and general medicine is described.

Calcium EDTA is effective and easily administered. It is recommended as the drug of choice in lead intoxication.

From the Authors' Summary.

The Use of Thermostatically Controlled Electric Heating Pads in a Maternity Nursery. C. Isbister and J. Isbister, M. J. Australia 2:879-882 (Dec. 12) 1954.

The use of the thermostatically controlled heating pad in the newborn nursery was found to give much better control of the infants' body temperature than hot water bottles.

McGuigan, Evanston, Ill.

Artificial Hibernation in Pediatrics: Its Application in the Toxic Infections of Infants. M. Crisalli, S. Scarabiochi, and A. Terraagna, Minerva pediat. 7:1318 (Oct. 27) 1955.

Laborit, a French clinician, initiated the work on artificial hibernation, accomplishing it by the action of certain drugs which affect the various hormonal activities and nervous reflexes. He was able to produce a state of hibernation, manifested by low metabolism, lowered body temperature, hypotension, slow respiration rate, analgesia, glandular hyposecretion (thyroid, pituitary, salivary, gastrointestinal), slowed peristalsis, diminished urinary secretion, low blood coagulability, leucocytosis, low azotemia, low-voltage electrocardiographic waves (as in myxedema), and the electroencephalographic waves as found in sleep.

In the present study, the drugs given to produce the hibernating state are Largactil (chlorphomazine), Fagan (promethazine), Hydergin (hydergine), and Mephedin (meperidine). They are given intravenously, the dose of each varying with the size of the child and the presenting symptoms. Largactil acts on the vegetative nervous system, is an antispasmodic, produces hypothermia, is a hypnotic, and is mentioned as producing a pharmacological lobotomy. Fargan is an anelgesic and antihistaminic. Hydergin is a vasodilator and aids in lowering the body temperature. Mephedin is used only with the older children for its analgesic effects. The infant passes into a quiet sleep with muscular relaxation, passes little urine, and has no bowel movements even if it had had diarrhea. The body temperature falls to about 32 C (89.6 F). The duration of the hibernation period is about one to two days. The pulse falls to 60 to 90, and the respiration rate is 20 to 30. Close watch over the patient is imperative so that untoward reactions can be counteracted. Various drugs are kept available for use as the symptoms indicate. Thus Prostigmin (neostigmine) is used for abdominal distention, barbiturates for convulsive tendencies, 4% glucose solution or blood plasma are used if there is hibernation, and heparin is usually needed to prevent thrombosis.

Hibernation was used in the present study in the treatment of nine infants, 48 days to 11 months of age, in a marked state of toxemia due to gastroenteritis. It was used only with infants "in extremis" whom clinical experience indicated were destined to die in spite of the accepted methods of treatment. In several of the cases the gastroenteritis was complicated by mastoiditis, pneumonitis, or myocarditis. Antibiotics were given in addition to the hibernation. No ice packs were needed to lower the body temperature. Seven of the children recovered; the two that died were benefitted by the hibernation but died some days later.

Hibernation seems to succeed in removing the toxic manifestations on the body organs, especially the nervous system. Its action is analogous to the effects obtained by the intravenous use of procaine.

Higgins, Boston.

ORAL ADMINISTRATION OF PROCAINE PENICILLIN IN CHILDREN. K. POLACEK and C. MELICHAR, Pediat. listy 9:46 (June) 1954.

The penicillin levels in the blood were examined following the administration of tablets containing 100,000 units of procaine penicillin (without amidopyrin). A satisfactory absorption of the antibiotic from the digestive tract was found, and the following dosage is proposed: in the case of infants, 100,000 units twice daily, in toddlers and preschool children, 100,000 units thrice daily, in school children, 200,000 units twice daily, with 0.3 gm. of anidopyrin.

FROM THE AUTHORS' SUMMARY.

THE DOSAGE OF CHLOROMYCETIN PALMITATE IN CHILDREN. HANS-OLOF MOSSBERG, Acta pædiat. 43:174 (March) 1954.

Parke-Davis palatable Chloromycetin palmitate was tested. It is easily taken by young children, in contrast to the extremely repulsive crystalline Chloromycetin (chloramphenicol). The absorption rate for Chloromycetin palmitate is slower than that for crystalline Chloromycetin, and the maximum blood concentration, which for crystalline Chloromycetin is obtained about two hours after the fasting administration, is not reached until one hour later for Chloromycetin palmitate. A further retardation of absorption takes place if the drug is not administered fasting. The maximum blood concentration of crystalline Chloromycetin is three times higher than the maximum values for the palmitate of the same dosage. Control experiments show that the Chloromycetin palmitate dosage should be three times greater than that of crystalline Chloromycetin in order to obtain the same maximum blood concentrations. For the maintenance of a lowest blood concentration of Chloromycetin, a Chloromycetin palmitate dose of 200 mg./kg. per 24 hours, administered in four doses, is required. In order to obtain a more rapid initial rise of the blood concentration the first dose of Chloromycetin palmitate should be given with a single dose of crystalline Chloromycetin (approximately 15 mg./kg.).

FROM THE AUTHOR'S SUMMARY.

BESNIER-BOECK SARCOID. C. HOOFT, G. CARPENTIER, and M. J. DELBEKE, Maandschr. kindergeneesk. 22:26 (Jan.) 1954.

Report is made of a case of Boeck's sarcoid in an infant, in which the first symptoms occurred at the age of 2 months.

Two years later lymph-node biopsy and the typical ocular involvement confirmed the diagnosis.

At the age of 4 a splenectomy became necessary, as the marked splenomegaly was the cause of a so-called "splenogenic" bone-marrow inhibition followed by anemia, leucopenia, and thrombopenia.

At the present time, enlargement of the liver and reticular fibrosis in both lung fields are the most prominent symptoms.

FROM THE AUTHORS' SUMMARY.

ARTIFICIAL HIBERNATION FOR USE IN TREATMENT OF CHILDREN'S AFFECTIONS. N. HAVENKAMP BEGEMANN, Maandschr. kindergeneesk. 22:136 (April) 1954.

A survey of the concept of artificial hibernation and some indications for this method in internal pediatrics are presented.

FROM THE AUTHOR'S SUMMARY.

News and Comment

Personal

Appointments at University of Louisville.—The following appointments were announced by Dr. Alex J. Steigman, Head of the Department of Pediatrics, University of Louisville: Dr. Joseph A. Little to serve as Physician-in-Chief for the Children's Hospital Division of the Department; Dr. William Curtis Adams as Pediatric Service Director for the Louisville General Hospital Division; Dr. Mary O. Cruise as Director of the Longitudinal Growth Study. Dr. Little is an Associate Professor in the Department; Dr. Adams, Dr. Cruise, and Dr. Falkner are Assistant Professors in the Department.

Death of Dr. John E. Gonce Jr.—Dr. John E. Gonce Jr., Professor of Pediatrics and Chairman of the Department at the University of Wisconsin Medical School since 1924, died suddenly of coronary thrombosis on March 25. He was 62 years of age.

General News

Cedars of Lebanon Hospital, Los Angeles.—The Cedars of Lebanon Hospital in Los Angeles, Dr. B. M. Kagan, Director, has recently been approved for two years of training by the Residency Review Committee for Pediatrics of the American Medical Association.

Announcements

Change in Site of Oral Examination.—The oral examination of the American Board of Pediatrics, originally scheduled for San Francisco on Dec. 7, 8, and 9, 1956, will now be held in St. Louis on the same dates.

Scholarships Founded by the Guigoz Company.—The Société des Produits Dietetiques Guigoz, whose headquarters are in Vuadens (Switzerland), has founded an international scholarship intended to enable a student or a physician to devote one school year to the study of infant and child feeding and nutrition problems.

The scholarship is to be awarded by a Jury appointed by the International Children's Centre (ICC), Paris. The Jury must include two representatives of the Guigoz Company. The scholarship may be divided between several candidates.

The Jury will select the holders of the scholarship among the persons who will have sent an application to the ICC (Château de Longchamp, Bois de Boulogne, Paris 16è).

The applicants are required (*a*) to send a *curriculum vitae* specifying their work concerning medical, biological, or social problems on feeding and nutrition of infants and children, (*b*) to be presented by one of their Masters, and (*c*) to state the training they should like to acquire or the studies they should wish to carry on with the help of the Guigoz scholarship.

The holder of the scholarship will be expected at the end of his scholarship time to send to the International Children's Centre a scientific or social paper on the subject which he will have studied during his special training period.

Institutes for Care of Premature Infants.—The Institutes for Physicians and Nurses in the Care of Premature Infants at the New York Hospital-Cornell Medical Center, under the sponsorship of the New York State Department of Health and the United States Children's Bureau, will begin their eighth year of operation in the fall of 1956. These Institutes are designed to meet the needs of physicians and nurses in charge of hospital premature nurseries and special premature centers, and of medical and nursing directors and consultants in state and local premature programs. The attendance at each Institute is limited to six physician-nurse teams. The program for physicians is of two weeks duration and that for nurses of four weeks duration. Participants pay no tuition fee, and stipends are provided to help cover expenses during attendance at the Institute. Institutes for the

1956-57 year are definitely scheduled to start on the following dates: Sept. 17, 1956; Nov. 5, 1956; Jan. 14, 1957. In addition, if the number of applicants is sufficient to warrant it fourth and fifth Institutes will be scheduled beginning March 11, 1957 and early in May, 1957. Early application for these Institutes is essential since plans are contingent on the number of applications received. Additional information may be secured by writing Box 143, Institute in the Care of Premature Infants, The New York Hospital, 525 East 68th Street, New York 21.

Annual Summer Clinics of Children's Hospital in Denver.—A comprehensive review of recent progress in pediatrics designed for general practitioners as well as specialists will be presented at the Eighth Annual Summer Clinics of the Children's Hospital in Denver on June 27, 28, and 29. Material of wide interest, with emphasis on patient evaluation, diagnostic methods of greatest value, and sound therapeutic advances will be presented for discussion. Guest speakers this year will be Dr. Harry Bakwin, Professor of Clinical Pediatrics, New York University, Dr. Thomas C. Moore, Associate in Surgery at the Indiana University Medical Center, Indianapolis, and Dr. Joseph C. Risser, Associate Professor of Orthopedics, College of Medical Evangelists, Los Angeles. Further information can be secured by writing the Chairman, Summer Clinics Committee, Children's Hospital, Denver 18.

Postgraduate Fellowship in Pediatric Cardiology.—A Postgraduate Fellowship in Pediatric Cardiology is being offered at the Childrens Hospital and in the Department of Pediatrics of the University of Southern California. The position will be available for the year beginning July 1, 1956. Candidates should have the equivalent of at least one year of pediatric training on an approved service at the residency level. Stipend for the position will be $3600 per annum.

Approval of Residency Programs in Allergy.—The American Board of Pediatrics, through its Subspecialty Board of Allergy, and the Council on Medical Education and Hospitals of the American Medical Association are developing a program for the approval of residency programs in allergy in preparation for certification in that subspecialty.

Applications for approval should be submitted to the Executive Secretary of the American Board of Pediatrics, Dr. John McK. Mitchell, 6 Cushman Rd., Rosemont, Pa.

Pediatrics Fellowship.—A new fellowship program designed to provide an opportunity for pediatricians to prepare for an academic career in pediatric education with an emphasis on the social science and psychological aspects of pediatrics will be initiated by the Department of Pediatrics of State University of New York Medical Center in Syracuse in the fall of 1956.

This program is intended to provide a background for research and teaching in the cultural, social, and psychological aspects of pediatrics. Ample opportunity for continuing experience in pediatric practice and teaching will be available. The program will be a highly individualized one in which the Fellows will have an opportunity to participate in conferences, seminars, and clinical experiences with faculty members in the fields of pediatrics, child psychiatry, psychology, social work, sociology, and anthropology. Opportunities to explore psychoanalytic concepts concerning child care and rearing will also be available.

The program provides for a three-year training period with the appointment of one Fellow each year, so that a maximum of three Fellows will be in training at one time. Candidates should have completed their residency training in pediatrics. This program is being supported by a grant from the Commonwealth Fund.

Inquiries are invited from interested persons and should be addressed to Dr. Julius B. Richmond, Chairman and Professor, Department of Pediatrics, State University College of Medicine, Syracuse 10, N. Y.

Books

BOOKS RECEIVED

The Rochester Regional Hospital Council. By Leonard S. Rosenfeld and Henry B. Makover. Price, $3.50. Pp. 204. Harvard University Press, 44 Francis Ave., Cambridge 38, Mass., 1956.

Campbell's Operative Orthopaedics. Ed. 3. Two Vol. By J. S. Speed and Robert A. Knight. Price, $40. Pp. 1103, Vol. I; 2124, Vol. II. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1956.

Adrenal Function in Infants and Children. By Lytt I. Gardner. Price, $6.75. Pp. 221. Grune & Stratton, Inc., 381 Fourth Avenue, New York 16, 1956.

Health Observation of School Children. By George M. Wheatley and Grace T. Hallock. Price, $6.50. Pp. 488, with 86 illustrations. McGraw-Hill Book Company, Inc., 330 West 42nd Street, New York 36, 1956.

Angiocardiographic Interpretation in Congenital Heart Disease. By Herbert L. Abrams and Henry S. Kaplan. Price, $11.75. Pp. 233, with 161 illustrations. Charles C Thomas, Publisher, 301-327 East Lawrence Ave., Springfield, Ill., 1956.

Hunterdon Medical Center. By Ray E. Trussell. Price, $3.75. Pp. 236, with 9 illustrations. Harvard University Press, 44 Francis Avenue, Cambridge 38, Mass., 1956.

Lues Connata. By Johannes Oehme. Price, DM 26. Pp. 114, with 51 illustrations. Georg Thieme, Hainstrasse 17-19 Aufgang C, Leipzig, Germany, 1956.

Roentgendiagnostik des Hufgelenks. By R. Glauner and W. Marquardt. Price, $13.60. Pp. 168, with 195 illustrations. Georg Thieme Verlag, Intercontinental Medical Book Corporation, New York 16, 1956.

The Office Assistant in Medical or Dental Practice. By Portia M. Frederick and Carol Towner. Price, $4.75. Pp. 351, with 55 illustrations. W. B. Saunders Company, West Washington Square, Philadelphia 5, 1956.

Accidents a Levures des Traitements par les Antibiotiques. By Pierre de Graciansky and Jean Delaporte. Price, 1,200 fr. Pp. 118, with 14 illustrations. Masson & Cie, Libraires de l'Académie de Médecine, 120, Boulevard Saint-Germain, Paris, France, 1956.

Clinical Recognition and Management of Disturbances of Body Fluids. Ed. 2. By John H. Bland. Price, $11.50. Pp. 522, with 109 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

Electrocardiography—Fundamentals and Clinical Application. Edition 2. By Louis Wolff. Price, $7. Pp. 342 with 199 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

Prenatal and Paranatal Factors in the Development of Childhood Behavior Disorders. By Martha E. Rogers, Abraham M. Lilienfeld, and Benjamin Pasamanick. Pp. 157, with numerous tables. The Johns Hopkins University School of Hygiene and Public Health, Baltimore, 1956.

Biologische Daten fuer den Kinderarzt. Ed. 2. Edited by Joachim Brock. Vol. I, Pp. 651 with 78 illustrations; Vol. II, Pp. 1183 with 177 illustrations. Springer-Verlag, Berlin, Goettingen, Heidelberg, 1954.

These volumes represent a new and enlarged edition of the work which appeared at first in 1932. In the new edition 25 co-workers contributed chapters pertaining to normal growth and development of the child. Some of the chapters are extensive and valuable monographs in their own right. The chapter on growth is discussed in the first 118 pages, supplemented by 14 pages of references. The chapter on chemical metabolism comprises 335 pages and 19 pages of literature. Another large chapter in the first volume deals with blood, plasma proteins, blood groups, iron, copper, and cobalt metabolism. Anatomical and physiological data concerning the cardiovascular and respiratory systems are extensively treated. The chapter on nutrition deals with milk, foods derived from plants and animals, vitamins, and fundamentals of infant feeding. Digestion and intestinal bacteria are also thoroughly discussed in the first volume. The second volume contains, in addition to the chapter on chemical metabolism, a discussion of energy exchange, temperature regulation, water, and acid-base metabolism. The anatomy and physiology of the urinary organs, of the skin, of the endocrine glands, and of the nervous system are treated in separate chapters. Among the new contributions the chapters on the electroencephalogram, hypothalamus, child psychology, and cerebrospinal fluid deserve mention. Immune reactions and statistical data pertaining to pediatrics are also treated in this volume.

It is obvious from this brief review that the scope of this book goes far beyond the field indicated in the title. It contains not only biological data for the pediatrician, but presents also entire chapters of physiology of childhood. It is not possible to evaluate here all the chapters and contributions in detail, but it can be stated that the book contains a wealth of information useful to pediatricians and other physicians.

The American and the European literature have been utilized by the authors, and the references following each chapter should be of great value to American readers in search of foreign pediatric contributions to this field. The references are mostly limited to the name of the author and the journal (volume, page, and year). The subject of the publication is cited only in references of books and monographs.

Prenatal and Paranatal Factors in the Development of Childhood Behavior Disorders. By Martha E. Rogers, Abraham M. Silienfeld, and Benjamin Pasamanick. Pp. 157, with numerous tables. The Johns Hopkins University School of Hygiene and Public Health, Baltimore, 1956.

A careful and convincing report of research designed to find out if one of the causes of behavior disorders in children can be related to prenatal or paranatal abnormalities of mother or offspring, such as bleeding, eclampsia, cæsarian section, prematurity, cyanosis, and convulsions. The answer is "yes." The 81 pages of text serve to document and qualify this reply. There are 140 references and an appendix consisting of 67 pages of additional tables.

The 1151 children with behavior disorders were those referred by teachers to guidance services of the Baltimore Department of Education. The 902 controls were taken from the same classrooms and were also matched for race and sex. The information about the children was obtained from hospital, school, and guidance records.

Among the conclusions are the following: (1) A significantly larger proportion of the problem children had birth weights of 2500 gm. or less. (2) A significantly larger proportion of problem children had a history of prenatal or paranatal abnormality of mother or child. (3) Within the group of problem children, most pronounced association with paranatal disorders was found in the case of the children who were "hyperactive," and "confused-disorganized." (4) The relatively poor families economically contributed more delinquent and the better-off families more confused-disorganized children.

As the authors point out, there are limitations to a retrospective study based on records kept by other persons for purposes apart from those of the study. The relationships found are important, however, and indicate the need for further research to elucidate mechanisms and to define more satisfactorily the nature of paranatal abnormalities which can result in cortical damage.

Cardiovascular Surgery. By Conrad R. Lam. Pp. 543. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia, 1955.

This volume contains the material presented during a symposium devoted to discussion of cardiovascular problems. No attempt is made to approach each subject from a purely didactic viewpoint. Rather, the format is that of a delightfully informal presentation of papers followed by a brief discussion.

An interesting series of papers is presented covering current advances in cardiac catheterization, electrocardiography in congenital vascular disease, and angiocardiography.

An excellent section is included dealing with problems of cardiopulmonary adjustment in the presence of intra- and extracardiac communications between the systemic and pulmonary circulations. Emphasis is properly placed on the dynamic role of the pulmonary vasculature in determination of magnitude and direction of shunts.

An extensive section is devoted to evaluation of surgical techniques and results in mitral and aortic valvular disease. Interesting panel discussions of problems of diagnosis and management of atrial septal defects and the present status of hypothermia in cardiac surgery are also included.

A thorough exposition is made of the low flow concept in bypassing the heart and lungs for the repair of intracardiac defects. A summary of data on 54 patients who had undergone total bypass for periods of 5 to 40 minutes is presented.

A final group of topics covering the surgical treatment of aneurysms and arterial occlusive disease rounds out the symposium. Included in this section is a discussion of current techniques of procuring and storing vascular grafts.

The book represents a lucid summation of the enormous amount of work currently in progress in the cardiovascular field. Thus, this rather small volume should prove most interesting not only to thoracic surgeons but to internists and pediatricians as well.

Splenin A in Rheumatic Fever. By Alvin F. Coburn, Lucile V. Moore, Judith Wood, and Mary Roberts. Price, $3.75. Pp. 87, with 5 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1955.

Splenectomy in a patient suffering from active rheumatic fever was followed within minutes after manipulation of the spleen by signs of fulminating rheumatic carditis. This led to a study of the effects of splenic extracts as related to rheumatic disease. Two fractions, splenin A, and splenin B, were reported to have antagonistic effects; the former decreased, while the latter increased, capillary permeability. The present book is a preliminary report of a therapeutic trial of splenin A in forty-seven acutely ill patients, in whom the disease varied in severity prior to treatment.

Manufacturing Problems, both in laboratory and bulk quantities, did not permit sufficient material to be produced to evaluate the efficacy of this product. Methods for isolation of the pure substance have not yet been developed. In fact, the potency of the material used in the investigation appeared to be low, and the assay procedure required simplification.

Unfortunately, the evaluation of the results was based on impression, and no direct control series for comparison was provided.

If the difficulties of production of splenin A are solved to yield a sufficient quantity of this substance, a well-controlled, carefully documented study may become feasible.

The Psychoanalytic Study of the Child. Volume 10. Edited by Ruth S. Eissler, Heinz Hartmann, Anna Freud, and Ernst Kris. Price, $7.50. Pp. 394. International Universities, Inc., 227 W. 13 St., New York 11, 1955.

This tenth volume of the "Psychoanalytic Study of the Child" continues to meet the high standards set in previous issues. All people who work with children will find the articles of interest, and child psychiatrists and others interested in theoretical aspects of analytic work will find this volume a necessity.

Articles have been placed in three sections, dealing with (1) "Problems of Ego Development," (2) "Genetic Problems," and, (3) "Problems of Psychosexual Development." Among the papers presented in the first section, Hartmann and Kris write on the problem of sublimation. Typical of papers in the second section are those by Greenacre of fetishism and Mahler on symbiotic child psychosis. In the final section are articles by Spitz, Frai-

burg, and many others. Of especial pediatric interest is the paper by Jessner and her group, on "Emotional Impact of Nearness and Separation for the Asthmatic Child and His Mother."

All pediatricians will find the clinical material described in all of the papers of extreme interest. This is truly an excellent book.

Mechanisms of Congenital Malformation. Proceedings of the Second Scientific Conference of the Association for the Aid of Crippled Children. Edited by Harold Wolff. Price, $3. Pp. 137, with 50 illustrations. Association for the Aid of Crippled Children, 345 E. 46 St., New York 17, 1955.

This small volume will be of interest and importance not only to pediatricians but to obstetricians, internists, specialists in other fields, nurses, social workers, educators, and even members of the lay public. The lucidity and clarity of arrangement are a tribute to the editorial committee, of which Dr. S. R. M. Reynolds was chairman and Mr. Harold Wolff the editor. The book was an outgrowth of a meeting called by the Association for the Aid of Crippled Children at which none of the 43 participants were to prepare papers. They were to "interchange current ideas, take new soundings and plot new directions for the future . . . and hope . . . that a cross-fertilization might be achieved. . . ." This was therefore a conference to explore frontiers and to discuss ideas for future investigations that might come out of a comparison of different experiences. The participants were men of repute from many countries, most of whom were gathered in this country for a biological symposium at Cold Spring Harbor, where they had given formal addresses. The present conference relieved participants of the necessity of preparing papers. They had no responsibility for publication and were unable to continue interchange of ideas and knowledge gathered in their various disciplines beyond the spontaneous (and limited) remarks made at the time of the conference. The proceedings recorded by stenotype were given their initial editing by Mr. Wolff, who sent his manuscript to the editorial committee for evaluation, corrections, and recommendations. The editor then placed the material assembled into a related and orderly sequence, weighing and editing extraneous matter not contributing to the central theme of the meeting. Because the book was also designed for a larger than medical audience, simplification of terminology was inserted when possible.

The material is rearranged into sections as follows: (1) "Physical, Chemical and Sociological aspects of the Fetal Environment," (2) "The Placental Barrier," (3) "The Fetus," (*a*) "Tissue Selectivity (the Blood-Brain Barrier)," (*b*) "The Internal Milieux (Adrenal Function, Blood, the Role of Vitamin-E)," (*c*) "Respiration, (Respiratory Patterns, Respiratory Mechanisms and Blood Cases, Summary)." The result is a concise, readable, clearly presented and interesting book which actually covers much more than the mechanisms of congenital malformations. Much pain has been taken to assemble a useful, accurate index which runs from "Abdomen, movements of" to "Zebra Fish."

Scurvy as a Skeletal Disease. By H. J. Van Wersch, M.D. Price, not given. Pp. 365, with 182 illustrations. Dekker & Van De Vegt, N.V., Utrecht-Nijmegen, Holland, 1955.

The author tells us that the studies presented in this monograph were carried out as a result of his observations on an extremely interesting case of scurvy in a seventeen-year-old girl. The clinical data and the x-ray changes are presented in some detail. The first section of the book deals with a fairly adequate historical review of adult and infantile scurvy together with short chapters on the experimentally produced disease and on the classic x-ray changes.

The major portion of the monograph is taken up with studies of experimental scurvy in the guinea pig and of experimental rickets in the rat. The author has applied certain histochemical techniques to demonstrate glycogen, mucopolysaccharides, and alkaline phosphastase activity. His hypothesis as to the defects in scurvy and rickets is based on the transformation of glycogen to Cori ester and then to glucose and phosphate. Phosphorylase is responsible for the first, alkaline phosphastase for the second of these transformations. Van Wersch tries to indicate that in scurvy there is blocking of these two enzymes, while in rickets there is activation. It is not clear to the reviewer how these hypotheses explain the defect in scurvy, i.e., the failure of bone matrix to be formed, or the defect in rickets, i.e., the failure of inorganic materials to deposit in the organic matrix of cartilage and bone. There are numerous illustrations showing the distribution of glycogen, alkaline phophastase activity, and mucopolysaccharide.

This volume should be of interest to the student of bone and its abnormalities. Save for the historical introduction to human scurvy, it offers very little as far as skeletal disease in infants and adults are concerned.

Advances in Pediatrics, Volume VIII. Edited by S. Z. Levine. Price, $8. Pp. 272, with numerous illustrations. Year Book Publishers, Inc. 200 E. Illinois Street, Chicago 11, 1956.

This current volume maintains the excellent standard set by previous additions of "Advances in Pediatrics."

Of particular interest to this reviewer were Dr. Horace Hodes' article on the "Etiology of Infantile Diarrhea" and Dr. Margaret H. D. Smith's paper on "Subdural Lesions in Childhood, with Special Reference to Infectious Processes." Dr. Hodes brings the subject of infantile diarrhea up to date with a discussion of the relative roles of pathogenic Escherichia Coli, Group D Beta-Hemolytic Streptococci, and the viral agents.

Dr. Smith has brought together her own experience and the recent literature on the occurrence of subdural effusions following meningitis as well as other infectious processes. This is a most timely paper since it reemphasizes the necessity for doing subdural taps on infants whose recovery from meningitis is delayed as evidenced by persistent fever, convulsions, or abnormal neurological manifestations.

Other monographs in this issue are the following:

"Isosexual Precocity in Boys Including a Case of Gonadotropin-Producing Teratoma" by Samuel Z. Levine, Henry L. Barnett, Madoka Shibuya, and Joan K. Barber.

"Sarcoidosis in Childhood" by John P. McGovern and Doris H. Merritt.

"Offspring of Diabetic and Prediabetic Mothers" by Herbert C. Miller.

"Prevention of Accidents in Childhood" by George M. Wheatley.

"Mental Deficiency" by Herman Yannet.

All in all this volume is an excellent one and should be in the library of every physician interested in children.

The Psychopathology of Children with Organic Brain Disorders. By Lauretta Bender. Price, $5.50. Pp. 151, with 23 illustrations. Charles C Thomas, Publisher, 301-327 East Lawrence Ave., Springfield, Ill., 1956.

This book is the fourth in a series by the same author, drawing from her own vast experience over the last 25 years and the knowledge and experience of Paul Schilder and other contributors from the Psychiatric Division of Bellevue Hospital in New York. Most of the material, presented in brief and concise form, has been published in individual papers in various journals in the course of the years, so that this volume can serve as a compendium to the hurried reader and as a reference work to the investigator.

Its practical value is enhanced by case reports, many of them with follow-up studies over long periods, and by the description of some tests and neurological entities rarely encountered. The viewpoint of the authors (Paul Schilder "was the author of about half the book and the other half directly reflects his point of view") as to the degree to which organic lesions form the etiological background to psychopathological disturbances and the specificity of their effects may not be shared by all. However, evidence in this field is purely observational. In many instances the persistence of brain damage cannot be proved except by history of trauma or illness, and the ensuing psychological disturbance may be considered a direct and specific reaction to the damage, a nonspecific reaction to some neurological trauma and/or damage plus a psychogenic disturbance or a psychogenic disturbance unrelated and coincidental to the history of trauma.

Until such time as improved methods will permit a more accurate analysis of such cases, the tremendous experience of the authors as transmitted in this book offers a good working hypothesis. The body-image concept and the Gestalt test as developed by the authors are certainly valuable diagnostic tools. Dr. Bender believes that if these techniques were given greater consideration they might lead to earlier and more accurate diagnosis of the underlying cause of some behavior disturbances, thus to reorientation of treatment methods or the application of preventive techniques.

In the last chapter, "The Psychological Problems and Their Management in the Brain Damaged Child," the author summarized the problem in 24 pages in a concise but very readable form.

Physiology and Pathology of Infant Nutrition. Ed. 2. By L. F. Meyer and Erich Nassau. Price, $11.50. Pp. 533, with 59 illustrations. Charles C Thomas, Publisher, 301 East Lawrence Avenue, Springfield, Ill., 1955.

This volume was translated from the German edition published in Switzerland. The authors are distinguished pediatricians in Tel Aviv, Israel, and in Afulah, Israel, respectively.

The book is intended as a "guide for the practicing physician and for the student." As such it is unnecessarily long compared to similar material which is well presented in current American texts. For the specialist in this field, the book is of value because it presents interesting experiences and attitudes of these leaders who formerly represented European and now represent Israeli thinking in this field. The book would be more useful if a bibliography were included and the index were more complete.

The translation carries some expressions which will appear strange to the English reader. "Eutrophy" a term for "normal" state of nutrition, was recently discussed in an editorial in the American Journal of Nutrition. Although Shigella and Salmonella infections, megacolon, pyloric stenosis, and cystic fibrosis of the pancreas are described, there is an interesting omission of a discussion of the celiac syndrome.

The book will be of interest to those specially concerned with infants' nutrition but cannot be recommended for the student or the average practicing pediatrician of this country.

Introduction to Virology. By Gilbert Dalldorf. Price, $3.50. Pp. 102. Charles C Thomas, Publisher, 301 E. Lawrence Ave., Springfield, Ill., 1955.

This little book of only 102 pages is a gem of conciseness and clarity. It accomplishes the goal of the author to introduce basic virus procedures to bacteriologists and pathologists. The book can also serve as an excellent introduction for clinicians. It is based upon lectures and laboratory exercises in a medical school.

The author is well qualified to present this subject, having worked in this field for many years. He is at present Director of the Division of Laboratories and Research of the New York State Department of Health in Albany.

Some references are given in the text. However, a more complete bibliography would give those interested considerable help in extending their horizons under proper guidance. This is particularly true of the first eight chapters dealing with the nature of viruses and diseases caused by viruses. Chapters 9 and 10 which deal primarily with technics provide good references.